ANALYSIS OF PROGRAM ACTIVITIES
NATIONAL INSTITUTES OF HEALTH
1954

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE
U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

U. S. National Institute of Arthritis and Metabolic Diseases,
Laboratory Research

Report of program activities.

The laboratory research activities in NIAMD encompass both basic and applied studies. The following highlights of research progress in 1954 make no distinction between these types of studies since there is no real line which divides the two. Basic studies are generally classified as such only because our knowledge is not sufficiently advanced to foresee their implications and applications.

Amino Acids are not only the basic building blocks for proteins but enter into metabolic reactions in many ways. Derangements in amino acid metabolism are found in human diseases such as cystinuria, phenylpyruvic oligophrenia and alkaptonuria. During the past year NIAMD scientists have contributed to our knowledge of amino acid metabolism on several fronts. Aspartic acid has been shown, for the first time, to be a precursor of asparagine and of homoserine. Histidinal has been shown to be a precursor for the biosynthesis of histidine. Two new enzyme reactions involving imidazole acetal phosphate were shown to be involved in the biosynthesis of histidine. One of these represents a new type of transamination reaction. A previously unknown enzyme has been found which is involved in the conversion of the amino acid tryptophan to the vitamin niacin. 5 and 7-hydroxytryptophan, -tryptamine and -(hetero) auxin were synthesized and some of the compounds identified with new metabolites of tryptophan. A chemical method has been developed to convert histidine via the new (allo)-hydroxyornithines to (allo) hydroxyproline (of interest as a constituent of connective tissue).

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Animals with diabetes have been found to be unable to convert tryptophan to niacin - a defect correctable by insulin. Methionine appears to diminish animals (chicks) requirement for vitamin B_{12}.

Amines - These substances are closely related to amino acids and are involved in many physiologic and toxicologic problems in health and disease. Histamine is a powerful substance which appears to be important in gastric secretion, in certain types of neural transmission, in allergy and anaphylaxis and in stimulating the pituitary-adrenal system. NIAMD scientists have studied systematically the biosynthesis and breakdown of this important amine. During the past year imidazoleacetic acid riboside was identified as a major intermediate in the metabolism of histamine. Spermine and related amines have been investigated since they are potent kidney damaging agents. Spermidine, putresine and an amino aldehyde have been identified as the breakdown products of spermine. An enzyme has been found which protects animals against lethal doses of spermine.

Proteins are not only a major structural element of all tissue but function in many ways as enzymes, hormones, immune antibodies, in blood coagulation and muscle contraction, in maintaining normal osmotic pressure, and as carriers of important substances. The processes by which proteins are arranged in an orderly fashion to form biological structures are being studied, for example, in muscle contraction and in blood coagulation. Two peptide fragments have been identified which appear during blood coagulation. ATP splitting and contraction of muscle fibers are not correlated as once thought. In addition to ATP and ITP, it has been shown that the inorganic salts KSCN and KI can cause muscle fibers and myosin threads to contract. Both human and bovine serum albumin were induced to polymerize reversibly under the influence of hydrogen ions and salts. The amino acid

lysine has been discovered in the reaction mixture. Lysine is not a component of ordinary proteins. A possible explanation is known glycolytic preparations which inactivate the agglutinin reaction contain traces of phosphate arthritis.

Carbohydrates are a major dietary and metabolic fuel and provide building blocks for the synthesis of many important metabolites and structural elements in tissues. An intimate understanding of carbohydrate metabolism is basic to improved methods of preventing and treating diabetes and many other diseases. High attention has been given to a relatively uncontrolled "alternate" pathway of carbohydrate metabolism. NADP reductase found that in liver about 1/3 of glucose is metabolized via the hexose monophosphate pathway. Hexose monophosphate appears to be utilized primarily via the "alternate" oxidative route. Some free and which were diabetic or fasted appeared to use the glycolytic pathway to a greater extent. Muscle from diabetes appeared to use the glycolytic mechanism exclusively.

Isolated nuclear systems have been used in elucidating the precise mechanism of the "alternate" pathway. 6-phosphate gluconate, isocitrate, 6-phosphate and phosphorylated intermediates have been definitely identified as all three are being involved in the release of carbohydrate metabolism. Oxidative metabolism, alpha-ketoglutaric acid, has been investigated.

Glycogen is a complex sugar which constitutes a major storehouse of quickly available energy. Although glycogen yields only glucose on basal hydrolysis, it is metabolically inhomogeneous. Glucose residues are added to or removed from the periphery of the molecule quite readily, but find their way into the central portions of the molecule more slowly by a continual process of branching.

Back to the above investigations on the method of the formation of carbohydrates which CAMO has conducted for many years. Six new oligosaccharides, heptoses, heptuloses and heptitols, and ribose orthoesters (derivatives of unknown structure were prepared and characterized; the structure of the carbohydrate moieties in stevioside, a non-toxic substance of plant origin which is 300 times as sweet as sugar, was determined. Hitherto unknown types of linkages were found in this molecule.

Vitamins - Substantial progress has been made in purifying factor 3 which protects against acute necrotic liver degeneration in animals. Concentrates of 10,000 fold purification can now be produced. An in vitro test for factor 3 has been developed. The immediate cause of death of animals with this disease has been found to be hypoglycemia and thereafter coma. A metabolic respiration defect in their livers (histologically normal) can be reversed in most experiments with vitamin E or factor 3. The earliest recognizable pathological finding in these livers is in the mitochondria.

Tentative evidence has been obtained for one or more unidentified growth factors in the crude. The amount of dietary fat has been shown to cause 4 fold differences in the vitamin B_{12} requirement of chicks. The anemia commonly observed in folic acid deficient rats has been identified as pernicious pteroic acid. N^{10}-formyl folic acid has been isolated and identified from liver. A labile reduced form of this compound may be present in human urine following folic acid administration. Large amounts of vitamin D decrease dietary requirements for riboflavin and pantothenic acid in dogs as previously shown for rats. Treatment of diets with ethylene oxide (sometimes used commercially) caused marked nutritional deterioration due in part at least to destruction of lysine.

[illegible] and to a lesser extent folic acid and valine. Chicken embryos [illegible] fat deficiency have been produced in guinea pigs for the first time for [illegible] deficiency signs characterized. Choline deficiency in the guinea pig differs from that in other species since no marked fatty livers were observed, no [illegible] hemorrhages were found but small haemorrhages in the adrenal and extramedullary tissue were noted.

Fat - Obesity has been induced in rats by high fat diets. These animals have been shown to have a very low tolerance to high dietary thyroid. Histological studies showed degeneration of the B cells of the anterior pituitary and corticoadrenals. The kidneys were 2 to 3 times normal size with haemorrhagic areas and pitted cortices. Testes and seminal vesicles were small and degenerated. Livers were enlarged and fatty in many instances. Obesity was also induced in mice by breeding ACTH producing tumors. Using fertile frog eggs in which the fat and protein was tagged with C^{14}, it was found that C^{14} activity in fat dropped as development progressed, while carbohydrate was stable. Drugs such as dinitrophenol altered this pattern and produced changes in protein to fat. Some evidence was obtained that guinea pigs may have a dietary requirement for fat per se in addition to needing essential fatty acids.

Minerals - The mechanism by which the body compartmentalizes various inorganic ions and fluid to maintain a relatively constant pH difference between fluid inside and outside of cells, and thereby permits many of these substances to be needed, is a fundamental characteristic of living cells. Using [illegible] in vitro model systems have discovered a mechanism which explains the accumulation of ions against a concentration gradient and have developed a theory to account for the differential accumulation of, for example, potassium over sodium ions

a resistance. The entry and exit of sodium, potassium and calcium in normal and has been studied in relation to nerve function under conditions of oxygen lack and in the presence of certain drugs. Previously unsuspected interrelations between sodium, potassium and calcium have been found in nutrition studies in rabbits. Extremely small amounts of copper have been found to be required for the conversion of pentose phosphate to a new pentose tentatively identified as an isomer of ketopentose.

Hormones - Several advances have been made in this field which are of direct interest to the research mission of NIAMD. A reliable method has been developed to assay thyrotrophic hormone and methods to assay adrenal hormones in body fluids have been developed. Hypersensitivity of the thyroid to stimulation by thyrotrophic hormone and ACTH produced tumors. Thyroxin has been shown to exert a major effect on protein formation. A new factor of thyroxin has been synthesized for testing as a possible antagonist to thyroxin. A method has been developed to study the action of insulin and anti-insulin substances in vitro.

A number of naturally occurring steroidal substances which might be possible precursors for the synthesis of cortisone have been isolated, studied chemically and their structure determined. Chemical rearrangements which might be involved in the conversion of steroids to other substances have been investigated and clarified. In other studies, methods have been developed to study the action of radiant energy on steroids and to isolate and identify the products of the reaction.

Glucuronic acid is of special interest since many toxic compounds, certain medicinals and hormones are excreted from the body in combination with this substance and it is an important constituent of connective tissue. A puzzle of long

steroids is that glucuronic acid administered exogenously does not participate in these functions whereas that manufactured in the body does. The validity of this fact in man was confirmed by NIAMD investigators using isotope tracer techniques. This puzzle seems about solved since the mechanism by which glucuronic acid arises in the body is such that glucuronic acid is produced in an "activated" form. A new enzyme, uridinediphosphoglucose dehydrogenase, was found which catalyzed the oxidation of uridinediphosphoglucose to uridinediphosphoglucuronic acid. The latter can serve to donate "active" glucuronic acid for conjugation and detoxification reactions. Other studies have shown that about 1/3 of the steroid steroids in plasma are present as glucuronides. Progress had been made in chemically synthesizing glucuronides of various steroids for use in research.

Enzymes and Coenzymes - Uridine nucleotides, referred to above, are a relatively new class of metabolic substances, which may have great significance. Uridine pyrophosphate N-acetylglucosamine and uridine pyrophosphate N-acetyl galactosamine sulfate were isolated from natural sources and may be key substances in the synthesis of glycoproteins and mucopolysaccharides which are of basic importance in relation to connective tissues and arthritis. In addition, scientists now obtained that uridine triphosphate may be involved in the contraction of muscle.

A technic has been developed whereby the important enzyme hyaluronidase can be localized and studied histologically in tissues using an antigen-antibody fluorescent dye procedure.

Two new enzymes have been reported which catalyze a new series of trans-phosphorylation reactions. A new deaminase has been obtained which rapidly converts adenosine to inosine. Two additional enzymes have been discovered which

most possible the simplification of pharmacological and immunological investigations in the determination of nucleic acid and the isolation of a nucleotide not identical with any known compound. An enzyme has been prepared from cell free extracts which catalyzes the conversion of glucose acid to glucose acid-6-phosphate.

Nucleic acids are complex materials consisting of nitrogenous bases, phosphates and a pentose sugar. They occur in all cells and are thought to provide the chemical basis of heredity. Important new information in this field has been secured by NIMH scientists. Enzymes have been found which are capable of synthesizing portions of these complex molecules. Hormone inhibitors have been discovered which could convert one nucleic acid into another. There are probably hundreds of different nucleic acids each with its own special function. These studies have also clarified many details as to the precise chemical structure of these substances. A new series of transphosphorylation reactions has been discovered which makes possible the synthesis of all the triphosphates which are believed to be precursors in nucleic acid synthesis.

Metabolic studies have shown that diabetes insipidus is marked by an increased glucose tolerance, sodium retention, potassium loss, acidic conditions and in some instances negative nitrogen balance. Continuous electric [illegible] transection of the spinal cord (between T.6 and T.7) was followed by similar changes. In other studies utilizing P^{32} labeled glycine, it was shown that patients with muscular dystrophy synthesized creatine at a normal rate but failed to introduce it into muscle cells at normal rate.

Magnesium sulfate and glutathione had a mutually potentiating effect in protecting against the reproduction inhibiting effect of radiation in hydra.

being compared in both fundamental and applied studies. In general, it was found that a process called "pore diffusion", hitherto described only in plants, was responsible for a large portion of their oxygen uptake. Other insects were found capable of impounding their respiratory CO_2 for long periods, only to release it in great gushes. The mechanism for this was found. Further progress was made in understanding the physiologic and pathologic (especially heart damage) effects of high altitude hypoxia. A type of nervecentricle was found also in these rats. Hypoxia did not serve as a stimulus to asynchronists to cold blooded animals such as turtles, now could this species make the circulatory and respiratory adjustments which warm blooded animals can. The respiratory physiology of underwater swimmers was also investigated. By studying oxygen consumption and determining the coefficient of oxygen utilization, it was found that an underwater swimming rate of 0.7 knots was most efficient although this efficiency did not exceed 5.1%.

Analgesics - The separation of pain relieving and addicting properties continues to be a goal of NIMH's chemistry and biologics. A number of new compounds were prepared, some of which appear promising. One compound in particular (3-(m-hydroxyphenyl) 3-methylpiperidine) has analgesic activity which may be surprise in animals but without the side effects characteristic of morphine. Quantities of the compound are being prepared for addiction studies. Important contributions were made to the chemistry and structure of compounds related to analgesics. Syntheses of potential new analgesic agents related to meperidine, morphine, and methadone have received particular attention.

Shock - Important additional data has been collected to new established the safety and efficacy of oral saline and soda in the treatment of burn shock

In animal studies, preliminary data suggests that the binding of sulfadiazine in solution to sodium is similar in humans and may be only important in therapy. The simultaneous use of the synthetic plasma expanders, dextran and PVP, is being studied in dogs to determine compatibility, effects on renal hemodynamics, possible tissue localisation and damage.

Microbes - WIAMD's pathologists have cooperated with numerous scientists in other institutes in various infectious disease investigations. Other projects are being conducted to concentrate, separate, and purify viruses by ultracentrifugraphic techniques. Several drugs have been found which are superior to sulfones in treating human leprosy. A saturated solution of sulfamethazine in drinking water appears to control coccidiosis in rabbits. A booklet was published on the identification of helminths and protozoa in laboratory animals. The incidence and pathological features of mycoplasmosis in dogs and cats are determined.

Microscopy - The visualization of living and dead matter at high resolution is an integral part of many research programs in this institute. Considerable progress has been made in devising or adapting chemical reactions to obtain more precise localization and identification of substances in tissues. For example, it was found that nerve cell melanin is different from other melanins. Histochemical enzyme localizations indicate a diversity of function as well as morphology in the several segments of the nephron. Some progress has been made in devising a histochemical technique to localize myocarin. Utilizing the very high magnifications of the electron microscope, it was found that a bacteriologic had a capsule composed of striated fibers rather than the expected gel. Certain bacteria revealed cell walls of perfectly ordered spherical macromolecules with flagella composed of helical structures showing an underlying regularity in macromolecular structure.

Toxicology - Iodides are a desirable solute in cooking salts and, when heat and humidity make iodide impractical. However, the safety of iodides is not established. NIAMD scientists have concluded the first portion of a study which, by extrapolating animal data to man, shows a large margin of safety in spite of the fact that iodates are more toxic than iodides. Thiosulfate and thiocyanate are effective in reducing iodate toxicity. Additional studies of iodates, particularly as to their methemoglobin producing tendency, will be necessary before final conclusions as to safety for man can be predicted. Toxic doses of iodates were shown to damage the parietal cells of the stomach and to stunt. A summary of the clinical toxicity of antibiotics has been made and prepared for publication. A book on the toxicity of halogenated hydrocarbons has been submitted for publication.

National Institute of Arthritis and Metabolic Diseases
Intramural Activities

The National Institute of Arthritis and Metabolic Diseases awards four intramural activities: 1) Grants-in-Aid for Research, 2) Research Fellowships, 3) Traineeships, and 4) Training Centers. The last named program was activated during the last two months of the year and at the end of the year no grants had been made.

Research Grants

At the end of the year there were a total of 438 active research projects representing a sum of $2,080,731. The distribution of these projects is as follows: Arthritis-69, Diabetes-69, Nutrition-36, Diseases of Blood-8, Allergy-12, Diseases of the Liver-11. Under the heading of Metabolism the following areas were represented: Adrenal Gland and Hormones-24, Thyroid Gland and Hormones-23, Kidney 14, Pituitary Gland and Hormones-17, Digestive Tract, including Pancreas,-13, Basic studies including Enzyme, Protein, Sterol, Phospholipid and Vitamin studies-56. The remaining miscellaneous studies were in the general endocrine disturbances, growth and development, and pregnancy.

During the past year particular attention has again been given to the stimulation of research in the fields of diabetes and arthritis. These areas have been particularly neglected in the past and it is interesting to note that funds from this Institute alone gave more support during 1954 to arthritis and rheumatic diseases than did all government and private agencies in 1950. In 1955 the National Institute of Arthritis and Metabolic Diseases supported 12 centers

projects in 4 weeks. The research projects have resulted in papers which are located in 25 cities and the District of Columbia. At the International of the American Rheumatism Association held in Bermuda in November 1956, over half of the papers presented were the result of studies supported by the funds of this Institute. It is, of course, apparent that we have at the present time no knowledge of the precise steps toward the ultimate solution of the problem of arthritis. It is possible, in fact--likely, that many projects that receive their support not only from this Institute but from other sources, which at present have no apparent relationship to arthritis may prove to be the key step in the ultimate victory over this disease. For these reasons our present classifications are obviously experimental.

Accomplishment Highlights

1. Many phases of clinical arthritis are being studied. The problem of getting the crippled arthritic back to work is one supported by this Institute which has been the subject of study. By means of intensive rehabilitation procedures, 31 of 41 patients severely disabled by arthritis, 13 have been discharged from the hospital; 6 of these are now self-sufficient. One has been placed. The other 7 are partially self-sufficient. Of 21 less severely disabled patients, all have been discharged from the hospital and 16 are self-sufficient, while 5 are partially so with an average increase of 16% in function. Seven of these last 5 patients have full-time jobs.

2. Of the projects dealing with fundamental studies of connective tissue, one in particular has brought out some interesting findings. A "building block" of connective tissue is the substance known as collagen. By chemical treatment of this material it has been possible to visualize through the electron-microscope

changes in its structure. Treatment with one chemical apparently destroys the material, but it can be restored to the previous unpolluted physical appearance by treatment of this solution with another chemical substance.

3. Advances have also been made in the study of joint fluid. In the past, all studies of joint fluid have been done on fluid which was been removed either from animals or from humans with damaged joints or from humans at autopsy. It has been thought to be impossible to be able to collect a sufficient amount of normal human joint fluid for physical and chemical studies. Using a simple technic, a group of investigators have finally hit upon a method to obtain fluid from the joints of normal living human subjects and have discovered in it a hitherto unidentified substance which is not present in the joint fluid of patients with rheumatoid arthritis nor in normal human sera. Studies to identify and learn the significance of this material are under way.

4. In the field of diabetes considerable attention is being paid to the natural course of the disease over a long period of time with particular reference to some of the degenerative complications. By these studies new knowledge is being gained of the natural course of the disease under various types of treatment. One team of investigators has studied 400 diabetic patients who developed diabetes during childhood, and who have had the disease for up to 30 years. Some of these patients have died, and of these, infection or diabetic coma have accounted for most of the deaths in patients who have had the disease less than ten years. Heart and kidney disease accounted for 40% of the deaths in patients who had the disease more than ten years.

5. The majority of individuals who develop diabetes in adult life are obese. Better understanding of the disturbances of the metabolism of fat and

Analysis of [illegible] Program Activities

January-December 1961

National Institute of Arthritis and Metabolic Diseases
Clinical Investigations

Adrenal Steroids

The past year has witnessed in this country and in Europe a resurgence of interest and vigorous research activity in the chemical, physiological and clinical aspects of adrenocortical steroids. The isolation and identification of aldosterone, the synthesis of radioactive hydrocortisone and cortisone acetate, and the development of better methods for the biochemical analysis of 17-hydroxycorticosteroids were chiefly responsible for these renewed efforts in endocrine scientific research. Scientists in Clinical Investigations at NIAMD have actively participated in this fresh assault.

Utilizing radioactive hydrocortisone and improved methods for biochemical analysis of 17-hydroxysteroids and 17-ketosteroids developed in this laboratory, the rate of endogenous production, turnover rate, physiological disposition and metabolic fate of hydrocortisone were determined both in the experimental animal and in man during health and disease. It was discovered that the adrenal cortex in normal man produces approximately 30 mg. of hydrocortisone daily, that the metabolic pool consists of 3 to 4 mg. and that this pool is turned over approximately ten times a day. Hydrocortisone in either pharmacological or physiological (trace) amounts was found to have a mean half-life in plasma following its intravenous infusion into normal subjects of 115 minutes. Cortisone disappeared from the plasma twice as rapidly as hydrocortisone (65 minutes). The rate of disappearance of hydrocortisone from the plasma was markedly delayed in patients with liver disease and was much accelerated in patients with hyperthyroidism. Metabolic

hydrocortisone administered to normal man in large quantities intravenously or orally was very rapidly excreted, almost entirely in the urine. Fifty percent appeared in the urine within the first six hours, additional 25% in the next 18 hours and 10% more in the following 24 hours. Only 5% appeared in the feces. Thus 95% of the administered radioactivity was recovered. No isotope was demonstrated after 96 hours and none appeared in the expired carbon dioxide.

The biological mechanism for inactivation of corticosteroids and cortisone in mammals has been defined by Brownie scientists. Enzymes have been isolated in the granule-free cytoplasm of the rat liver which convert adrenal steroids to their inactive "tetrahydro" form. Two enzyme systems are involved in this process. Enzyme I reduces cortisone to dihydrocortisone, possesses low activity and requires TPNH as a co-factor. Enzyme II completes the process and mediates the reduction of dihydrocortisone to tetrahydrocortisone. The enzyme system can utilize either TPNH or TPN as a co-factor and in contrast to the first system is very active and lacks specificity, reducing other dihydrosteroids besides dihydrocortisone.

In addition, the manner in which the reduced tetrahydro corticosteroids are subsequently conjugated as their glucuronides has been elucidated. Uridine diphosphate glucuronic acid has been found to be the active glucuronide donor for this process. This co-factor is present in mammalian liver and with the aid of an enzyme found in the microsomes of hepatic cells transfers the glucuronic acid to the steroid. Purification of the enzyme and studies as to its specificity are under investigation at present. It is apparent that uridine diphosphate glucuronic acid serves as a co-factor in the formation of many other glucuronides and is therefore of paramount biologic importance.

Steroid chemists have repeatedly demonstrated that an intimate relationship exists between the chemical structure of adrenal steroids and their physiological properties. Clinical investigators found, in addition, a very close correlation between the structural formula and the therapeutic capabilities of these hormones. The addition, removal or transfer of a single atom or arrangement in the corticosteroid molecule may effect a drastic change in its clinical effects or indeed its therapeutic potency.

Unremitting efforts have been made by the synthetic chemists to produce a steroid possessing high anti-inflammatory or antirheumatic potency. Two such compounds, metacortandralone and metacortandracin, were submitted to WHO for clinical trial and evaluation in August and October 1954. Treated in 12 patients with rheumatoid arthritis who failed to improve with cortisone, hydrocortisone, corticotrophin, gold compounds or phenylbutazone, the new steroids induced a spectacular clinical response in all but two. These two patients had rheumatoid arthritis with irreversible deformities changes in many joints. Even they showed definite but not dramatic improvement. The new steroids were found to be 3 to 4 times the potency of cortisone or hydrocortisone. This additional potency was not accompanied by a corresponding increase in the severity or frequency of undesirable side-effects. It was demonstrated that these steroids possessed unique physiological properties of adrenocortical hormones. It is planned to organize clinical trial of these additional steroids as they are synthesized or isolated provided there is evidence to believe from preliminary studies on animals that they may have anti-inflammatory properties.

Connective Tissue Metabolism

Although rheumatoid arthritis is clinically the most important of the diseases affecting joints little is known today of its underlying pathogenesis. The structures of joints are made up of connective tissue rather complex characteristic sugars rich in hexosamine. Institute scientists have discovered that isolated fragments of connective tissue retained their capacity to produce hexosamine. They have further shown that the concentration of hexosamine in connective tissue is directly influenced by hormones secreted by the thyroid and anterior pituitary glands. They have also collected important information concerning the nature of some of the changes observed in disease processes and may lead to a better understanding of the pathogenesis of certain rheumatic diseases, especially rheumatoid arthritis. New techniques have been developed during the course of these studies which may help provide more information along these lines.

Specific Serological Test for Rheumatoid Arthritis and the Nature of the Factors Involved

A test proven useful in the diagnosis of rheumatoid arthritis depends upon the capacity of serum from such patients to agglutinate sheep red blood cells. This serological test has been refined to that it is found it is positive in about 90% of the patients. In the course of study relating a specific agglutination factor in serum from arthritic patients it was discovered that these sera lacks an agglutination inhibitor found in the euglobulin fraction of normal plasma protein. The activity of this inhibitor has been matched with a simple synthetic polypeptide which, when injected into patients, partially reverses the agglutination reaction. This abnormality in the constitution of the plasma proteins in patients with rheumatoid arthritis is being further explored to ascertain whether, by its reversal, a remission in the disease process can be brought

Results

The life expectancy of the red blood cell, another topic central to the present subject, has in the past been estimated by the Ashby technique. This procedure, involving a transfusion of blood from another donor, involves hazards of transfusion reaction as well as inadequate serum separation. Investigators have perfected a far simpler and safer technique involving the withdrawal of a small sample of the patient's blood, tagging of these red cells with radioactive elements, and reinjection of these labeled red cells into the same subject. Clearly the understanding of the mechanisms leading to anemia, in any circumstance, requires accurate knowledge of the viability of the red cells and this knowledge is now readily available. A hitherto unrecognized difference between man and rabbit in this regard has already been brought to light.

Discussion

The salient renal disturbance has been polyuria[illegible]. In this instance, attributable to a relative or absolute deficiency of insulin. The most important disturbance metabolically is of the utilization of fatty acids[illegible]. Improved diagnostic, prophylactic and therapy must rest upon an increasingly precise understanding of the defects underlying the disease. As a result, considerable local and structural relationships of the several organs are clearly shedded. At an enzymological level, the metabolic pathways whereby sugar is converted into other products and is ultimately burned in the body are being investigated. A novel route of glucose oxidation, hitherto but vaguely outlined, has been systematically explored and outlined by Institute scientists. The hormonal mechanism of sugar storage in the animal is under investigation by our endocrinological studies are directed toward a clearer understanding of the

relationship of insulin and its antagonists, and a program has been developed designed to clarify the nature of anti-insulin agents which occur in the blood of some diabetic patients. Finally the metabolism of those cells of the pancreas responsible for insulin production is to be studied, in the hope of finding an explanation for their curious and unique function.

Thyroid Function and Disease

It has been found by Institute scientists that the normal liver is capable of removing a large amount of the protein bound iodine circulating through it as determined by comparison of arterial and hepatic venous blood. Thyroid homogenates have been found to have the ability to utilize iodide converting it to monoiodotyrosine and, especially, to an intermediate which has been found to be extractable by carbon disulfide. These studies represent two approaches to normal aspects of thyroid physiology and disease. These include the mechanism of hormone synthesis in the normal and diseased thyroid, the role of the liver in thyroid hormone metabolism, and the role of the specific thyroxine-binding protein in thyroid physiology.

PHS-61 A-2

[illegible] Institutes of Health
Application for Grant

1. ITA(N)-5(C)3-C
SERIAL NO.

2. BUDGET DATA:

	ESTIMATED EXPENDITURES	REQUESTED POSITIONS			FOR USPHS			RECOMMENDED BY
		GRADE	OTHER	TOTAL	GRADE	OTHER	TOTAL	
FY 1955	10,500	2/3	6/3	1 1/3	2/3	2/3	1 1/3	
FY 1956	10,500	2/3	6/3	1 1/3	2/3	2/3	1 1/3	

3. RESEARCH ACTIVITIES:

RESEARCH [X] CONSTRUCTION [ ]

REVIEW & EVALUATION [ ] TRAINING (INCLUDING [illegible]) [ ]

4. IDENTIFY ANY CORRESPONDENCE UNDER (1) THE PUBLIC HEALTH SERVICE, OR ANOTHER [illegible] AGENCIES, PERTAINING TO[illegible], OR PROPOSED FOR THIS PROJECT DURING [illegible] 1955 or 1956. IF CORRESPONDENCE HAS BEEN WITH THE LOCALITY WHERE THIS [illegible]

None

5. IF THIS PROJECT REQUIRES, CONTEMPLATES, OR PARALLELS RESEARCH BEING CONDUCTED BY THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), CURRENTLY SUCH RESEARCH: (BY SERIAL NO.(S) IF KNOWN) [illegible]

None

AIAID-6013-1

SERIAL NO.

LIST PUBLICATIONS ISSUED THAT RESULTED FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

LIST TITLES AND AUTHORS OF THESES SUBMITTED BY THIS PROJECT DURING CALENDAR YEAR 1954:

None

Laboratory of Biochemistry and Nutrition

(Project Description Sheet)

NIAMD
INSTITUTE

3. Laboratory of Biochemistry and Nutrition
LABORATORY OR BRANCH

Biochemistry & Physiology of Nutrition
SECTION

4. _____
LOCATION (IF OTHER THAN BETHESDA)

NIAMD-6201.3-C
SERIAL NO.

Diabetes and Starch Metabolism Studies
PROJECT TITLE

E. G. Ball and W. L. Bencze
PRINCIPAL INVESTIGATOR(S)

None
OTHER INVESTIGATORS

PROJECT DESCRIPTION - Studies with rats on 6 vitamin diets are being continued on the importance of B6 in health and in metabolic conditions.

A. Alloxan diabetic rats appear to be unable to convert tryptophan to niacin as judged by their failure to maintain normal levels of urinary N-methylnicotinamide (MNA) following tryptophan (T) dosage, although they do respond following dosage with niacin, nicotinamide, or MNA. Control of diabetes with insulin leads to a normal T to MNA conversion. Feeding of fructose to diabetic rats ameliorated the signs of diabetes but did not improve the T to MNA conversion. The conversion of nicotinamide to MNA appears to be impaired in some diabetic rats but not to the extent the T to MNA conversion is affected. Administration of T to diabetic rats resulted in elevated blood sugar curves.

Rats made diabetic by other means will be investigated to determine whether they too show an impaired T to MNA conversion. Attempts will be made to determine the nature of this metabolic defect more precisely. Experiments are underway to find whether human diabetics exhibit a defect in T metabolism similar to the rat.

B. 3-Acetylpyridine (3-AP) (a niacin antagonist) studies have been continued in dogs and rats. The dog studies have shown that 3-AP acts either to replace niacin or as an antagonist depending on dosage and the nutrition of the dog.

with respect to niacin. Normal and niacin deficient dogs convert 5-HP to niacin as shown by CO2 excretion and the prevention and treatment of black-tongue. Niacin deficient dogs appear less able to make this conversion. Derived basic symptoms, including multiple paralyses, sometimes result when 5-HP is given to niacin deficient dogs, or with large doses to normal dogs.

Pathological examinations are being conducted, especially on brain and spinal cord, to determine the basis for the paralyses noted above.

In rats, experiments have been conducted to determine whether the lack of ability to convert 5-HP to niacin is specific for niacin deficiency. To date the conversion of 5-HP has been tested in riboflavin, pyridoxine, calcium pantothenic acid and niacin deficiencies. Only with niacin deficiency have the animals unable to make the conversion.

C. The role of corn in the etiology of pellagra is being approached by studying the effect of alkali treatment on the "availability" of niacin and the nutritive value of corn in studies with dogs. Corn is being treated under various conditions with Ca(OH)2 or NaOH. Other appropriate work upon any of these treatments seems to increase the supply of niacin as judged by CO2 excretion. This finding will be checked by studies on the prevention of blackTongue in dogs. Treatment of whole corn with lime (Ca) in the absence of moisture (which is the method now commonly used) does not produce the same effect.

NIAMD-62113-2
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	SUPPORTED POSITIONS: PROF	SUPPORTED POSITIONS: OTHER	SUPPORTED POSITIONS: TOTAL	MAN YEARS: PROF	MAN YEARS: OTHER	MAN YEARS: TOTAL	PROPOSED JULY
FY 1955	14,300	1/3	2 1/3	2 2/3	1/3	2 1/3	2 2/3	
FY 1956	14,300	1/3	2 1/3	2 2/3	1/3	2 1/3	2 2/3	

BUDGET ACTIVITY:

(RESEARCH) [X] (DEMONSTRATION) [ ]

(TESTING & APPROVAL) [ ] (TECHNICAL ASSISTANCE) [ ]

IDENTIFY ANY COOPERATING UNITS OR THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR WORK PROPOSED IN SECTION 1955 or 1956: IF COOPERATING UNIT IS WITHIN PHS PROVIDING SERVICE, NOTE [illegible]

None

IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

P.H. - 3

Contents of ARS Progress Report

Honors, Awards, and Publications Sheet

NIAMD-SERIES-C

SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Niacin and Anti-niacin Activity of 3-Acetylpyridine in Dogs. J. G. [illegible], S. N. Hundley and W. H. Sebrell, J. Nutrition (in press) (1955).

LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

NIAID
INSTITUTE

Laboratory of Biochemistry and Genetics
LABORATORY OR BRANCH

Biochemistry & Physiology of Nutrition
SECTION

NIAID-62213-5
SERIAL NO.

Vitamin and Amino Acid Metabolism
PROJECT TITLE

T. S. Daft
PRINCIPAL INVESTIGATOR(S)

M. Gregg, M. L. Tuzzio
OTHER INVESTIGATORS

PROJECT DESCRIPTION

A. Vitamin Sparing Factors

Previous work has shown that large amounts of dietary vitamin C or small amounts of certain antibiotics have the ability to decrease rat's vitamin B12 requirement by a factor of 3 or more. Current work is directed toward determining the mechanisms of these effects using various routes of administering the substances, vitamin balance techniques, and dietary manipulations. It has been found that penicillin administered parenterally finds its way into the gastrointestinal tract via the bile. Techniques have been developed to divert biliary secretions from the intestinal tract as an approach to determining whether penicillin exerts their vitamin sparing effect in the G-I tract or in the tissues. Other studies have shown that whatever the mechanism may be, large amounts of dietary vitamin C result in an increased supply of certain B vitamins in tissues. This work may have considerable significance in elucidating the various factors which influence vitamin requirements, as well as throwing considerable light on vitamin metabolism.

B. Histidine-Folic Acid Metabolism

Previous work has shown that folic acid deficient rats excrete a unique compound which has been isolated and tentatively identified as formimino glutamic

acid and that this compound arises from the amino acid histidine. Current work is directed toward defining the conditions under which this compound is excreted, especially with low tests of histidine, as an approach to develop a biochemical test for folic acid deficiency and to the mechanisms which prevent folic acid deficient animals from completely metabolizing histidine.

C. Metastatic Calcification in Mice

C3H mice fed a purified low protein diet develop calcified lesions in heart, muscle, arteries and lungs. The influence of various dietary supplements and dietary modifications are being studied to determine the etiology and pathogenesis of this syndrome. It has been shown that calcification is greatly lessened by increasing dietary protein and by certain supplements. These experiments may shed light on certain types of arteriosclerosis and possibly on unknown nutritional factors.

Analysis of Research Resources

Project Data Sheet

1. NIAMD-02113-3
GENERAL CO.

2. BUDGET DATA:

	ESTIMATED EXPENDITURES	DURATION REQUESTED			GRANT YEARS			PROJECT PERIOD
		DIRECT	INDIRECT	TOTAL	DIRECT	INDIRECT	TOTAL	
FY 1955	$5,200	-	3%	3%	-	3%	3%	
FY 1956	$5,200	-	3%	3%	-	3%	3%	

3. BUDGET AUTHORITY:

RESEARCH [X]

OTHER (Explain) [ ]

4. [illegible]

5. [illegible]

6. [illegible]

Analysis of the Immune Antibodies

Honors, Awards, and Publications Sheet

NIAMD-6211-03

SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"Excretion of a Histidine Metabolite by Geo Bab", H. Silverman, W. [illegible] and F. S. Daft, Proc. Soc. Exper. Biol. Med. 87: 451 (1954).

"Isoglutamine and the Growth of Lactobacillus Arabinosus" H. Silverman, E. [illegible] Rosine and F. S. Daft, J. Bact. 68: 98 (1954).

"Pantothenic Acid" Parts of Chapter 21 in Sebrell and Harris's "The Vitamins", G. H. Briggs and F. S. Daft, Vol. II., pp. 620-630, 632-637, 685-697, Academic Press, Inc., New York (1954).

LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

Awards and Honors, and Publications Since

Degree, Awards, and Publications Since

NIAMD-6210 5-3

SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS FUNDED PROJECT DURING CURRENT YEAR:
1954:

"Excretion of a Histidine Metabolite by the Rat", R. Gillespie, D. A. Drummond, and F. S. Daft, Proc. Soc. Exper. Biol. Med. 87, 451 (1954).

"Isoglutamine and the Growth of Lactobacillus Arabinosus" R. Gillespie, C. H. Rhodes and F. S. Daft, J. Biol. 68, 98 (1954).

"Pantothenic Acid" Parts of Chapter II in Sebrell and Harris's "The Vitamins", G. H. Briggs and F. S. Daft, Vol. II., pp. 426-530, 531-669, 668-697. Academic Press, Inc., New York (1954).

LIST HONORS AND AWARDS TO RESEARCH WORKERS ON THIS PROJECT DURING CURRENT YEAR 1954:

None

2. NIAMD
INSTITUTE

4. Laboratory of Biochemistry and Nutrition
LABORATORY OR CLINIC

3. Biochemistry & Physiology of Nutrition
SECTION

5. [redacted]
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD-60219-4
SERIAL NO.

6. Nutritional Improvement of Cereals
PROJECT TITLE

7. J. E. Knoblock
PRINCIPAL INVESTIGATOR(S)

8. L. D. Ing
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Previous animal experiments in this and other laboratories have demonstrated that amino acids lysine and threonine significantly improve the nutritional value of wheat, wheat, rye, bread and various "poor" dietary hybrid of Mexican origin.

Current work is directed toward finding food products which could be supplemented with lysine and threonine to complement their cereals. Particular attention is being paid to the problem of threonine since lysine can be produced cheaply by synthetic means. A dried alga (Scenedesmus obliquus) has appeared very promising as a predominantly source.

The significance of this work relates to the possible improvement of the predominantly cereal diets consumed in large sections of the world where protein undernutrition is especially prevalent. The effect of lysine and threonine supplements in human diets is being explored (see item 13).

NIAMD-62113-04
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS: PROF	OTHER	TOTAL	MAN YEARS: PROF	OTHER	TOTAL	PROGRAM CHIEF
FY 1956	12,800	½	1 1/6	1 2/3	½	1 1/6	1 2/3	
FY 1956	12,800	½	1 1/6	1 2/3	½	1 1/6	1 2/3	

BUDGET ACTIVITY:

ORIGINATION [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TERMINATION [ ]

NUMBERS AND DESIGNATING NAMES OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS PROVIDING FUNDS, FACILITIES, OR PERSONNEL TO BE UTILIZED IN CARRYING OUT THE PROJECT; HOW IT IS TO BE USED WITH ESTIMATE SERIAL NO.(S) (USE ADDITIONAL SHEET IF NECESSARY):

Dr. M. J. Krauss, University of Maryland (Algae studies)

Clinical Studies of Lysing and Screening Supplemented Milk Diets (with Dr. H. Sandstead) NIAMD - 62113-105

IF THIS PROJECT RESOURCES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH (BY SERIAL NO.(S) IF WITHIN NIH):

None

Appendix C of the Progress Report

Honors, Awards, and Publications Sheet

NIAMD-5211-4
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

LIST HONORS AND AWARDS TO PERSONNEL ASSIGNED TO THIS RESEARCH PROJECT DURING CALENDAR YEAR 1954:

None

Project Description Sheet

VIRGO	2. Laboratory of Biochemistry and Nutrition
INSTITUTE	LABORATORY OR BRANCH
Biochemistry & Physiology of Nutrition	4.
SECTION	LOCATION (IF OTHER THAN ARCHIVES)
NIAMD-62113-5	
SERIAL NO.	

Nutritional Aspects of Growth and Longevity
PROJECT TITLE

J. M. Hundley
PRINCIPAL INVESTIGATOR(S)

R. B. Ing, Dr. O. Michelsen
OTHER INVESTIGATORS

PROJECT DESCRIPTION: Animal Studies

The purpose of the study is to relate rapidity of growth to the composition of the body, to the development of disease and to longevity. Diets were utilized to produce planes of growth varying from severe retardation to very rapid. One strain of animals was being used, one is presently discarding which is not expected to become obese, and the other is a rapidly growing strain which is expected to become obese.

The study is expected to require 3 years and has not progressed far enough to yield major findings except to state that the weight alone does not indicate the desired planes of growth as determined by carcass analysis. A method has been developed to estimate body fat in rats by specific gravity.

The significance of the project relates to the influence of diet in cancer and the degenerative diseases and to influences of growth during childhood on maximal adult health and longevity.

Clinical Studies

Height-weight-age-sex-color-economic class data have been obtained on 10,773 6 to 8 year old children who were in the public schools in Philadelphia between

1965 and 1967. The data have been analyzed with the following results: [illegible] from good socioeconomic areas were consistently taller and heavier [illegible] from less favored areas. All groups of children showed a significant secular [illegible] in growth. Alterations in growth patterns and in attained heights and [illegible] found in the depression years of the 1930's.

The significance of this study relates to the possibility of using periodic height-weight measurements on children to yield a continuing index of nutritional status in this country.

It is planned to broaden the study to relate the pattern of growth during childhood to adult obesity, disease and longevity.

P.H.S. - 2

Analysis of the Program Activities

Program Data Sheet

4. MIAMD-63113-5
SERIAL NO.

5. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			ACCURACY DATE
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	13,600	½	2 2/3	3 1/6	½	2 1/2	2 5/6	
FY 1956	20,300	½	3	3½	½	3	3½	

6. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

7. IDENTIFY ANY COORDINATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1955 or 1956. IF COORDINATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S). (FY 1956)

Dr. E. Weaver and R. C. Taber - Philadelphia Board of Education (Problems with Children)

8. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH BEING ACCOMPLISHED IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH. (BY SERIAL NO.(S) IF WITHIN NIH)

None

NIAMD-5211-5
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"Diseases Due to Vitamin Deficiency and Malnutrition" W. H. Sebrell, R. S. Harris and J. M. Hundley. Chapter 24 in Beeson's Fundamentals of Internal Medicine, 1st Edition, Appleton-Century-Crofts, Inc., New York (1954).

"Malnutrition" W. H. Sebrell and J. M. Hundley, Chapter 13 in Brightman's Geriatric Medicine, 3rd Edition, J. B. Lippincott Co., Philadelphia (1954).

"Niacin" J. M. Hundley, Chapter 10 in Sebrell and Harris The Vitamins, Academic Press Inc., New York (1954).

"The Importance of Nutrition" J. M. Hundley, J. Home Econ. 46: 307 (1954).

"Evaluation of Nutritional Status of Population - Introduction and Summary Statement" W. H. Sebrell and J. M. Hundley in "Symposium on Nutrition Education and Status", National Research Council, Washington, D. C. (In press) (1954).

"Joseph Goldberger - A Biographical Note", J. M. Hundley, Public Health Reports 68: 738, Aug. (1953).

"Preventive Geriatrics, Comments on Nutrition", J. Mendigal State Med. Soc. 102: 824, May (1954).

"Balanced, Varied Diets Are Basis for Good Nutrition" Conclusions of a Symposium, J. M. Hundley, Pub. Health Reports 69: 855, Sept. (1954).

"Nutrition and Public Health" J. M. Hundley, Public Health News 35: 401, Dec., (1954).

"Significance of Blood Levels of Various Nutrients" J. M. Hundley, Proc. Third Community Nutrition Institute, Syracuse Univ. (In press) 1954.

"Nutritional Needs of Institutionalized Patients" J. M. Hundley, J. Am. Pub. Health Assoc. (In press) (1955).

"Niacin and Anti-Niacin Activity of 3-Acetylpyridine in Dogs" T. G. Hennessy, W. H. Sebrell and J. M. Hundley, J. Nutrition (In press) (1955).

LIST HONORS AND AWARDS TO PERSONNEL RELATED TO THIS PROJECT DURING CALENDAR YEAR 1954:

Fleming Award (Dr. Hundley)

Councillor to American Institute of Nutrition (Dr. Hundley)

Project Description Sheet

1. National Institutes of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Biochemistry and Physiology of Endocrine Glands
SECTION

4. Bethesda
LOCATION

5. NIAMD-BCNU-6
PROJ. NUMBER

6. Effect of hormones on muscle and milk proteins and on carbohydrate metabolism
PROJECT TITLE

7. Dr. Robert O. Scow
PRINCIPAL INVESTIGATOR

8. Gavin A. Hogan
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine the influence of hormones on carbohydrate metabolism and on the protein in muscles and milk of lactating rats.

Methods Employed: Various endocrine glands are removed from young experimental animals (rats, mice, guinea pigs). Some of these animals are treated with a variety of hormone preparations. At the end of the experiment the animals are killed and appropriate measurements made. Selected muscles are rapidly excised, freed of connective tissue, powdered, and then extracted with a salt solution. Individual protein fractions are produced by precipitation procedures. These proteins are estimated using a variety of staining agents.

Glucose tolerances (oral and intravenous) were made in normal and thyroidectomized rats, some of which had been treated to increase their body weights. The food intake of some normal rats was restricted so that the rate weights was the same as the hypophysectomized animals.

Major Findings: Thyroxine has a marked influence on protein formation as shown by the increase in body weight and muscle protein content of hypothyroidized rats injected with this hormone.

Both oral and intravenous glucose tolerances of thyroidectomized rats were impaired. There was no effect of food intake on body size on the oral and intravenous tolerance curves in normal and hypothyroidized rats. The maximum blood glucose level in hypothyroidized rats during the oral test was 50% above that of normals, possibly due to

3. PROJECT DESCRIPTION - Continued

impaired rate of glucose removal from the blood. The lower glucose removal rate during the intravenous test was almost the result, presumably due to a delay in urinary glucose excretion.

Preliminary evidence indicates that when young rats are given no food for 60 hours, there is a substantial decrease in the percentage of myosin in muscle, with none of the other muscle proteins showing a similar change.

Significance to NIAMD Research: Since a number of metabolic diseases are associated with marked disturbances of cell protein formation, it is important to know the factors that influence muscle growth and formation. Disturbances in the growth of collagen, one of the proteins studied in this project, occur in arthritis and in a number of other diseases.

Proposed Course of Project: Hearts, veins, and nervous analyses will be performed on hypophysectomized rats treated with growth hormone, corticosterone, or both, and on untreated control animals. The influence of corticosterone on the muscle content of phosphocreatine will be studied. Studies will be made on the effects of fasting, both the complete withdrawal of food and partial starvation, on the changes in muscle protein composition.

10. [illegible]

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	PROFESSIONAL PERSONNEL			OTHER PERSONNEL			PROJECT DIRECTOR
		FTE	OTHER	TOTAL	FTE	OTHER	TOTAL	
FY 1955	17,300	1	2 1/3	2 1/3	1	1 1/3	2 1/3	
FY 1956	17,300	1	1 1/3	2 1/3	1	1 1/3	2 1/3	

12. SUBMIT ACTIVITY:

RESEARCH ☐ [illegible]

[illegible] ☐ [illegible]

13. [illegible]

Approved for Unrestricted Release, IC, [illegible]
Radiation Branch, NCI
Radiobiology Branch, NCI

14. [illegible]

None

15. [illegible]

16. [illegible]

Soon, B. O. "Effect of Thyroxine on the Weight and Composition of Muscle, Fell and other Tissues in Young [illegible]". [illegible] 30, 1954

Soon, Robert O., and Jerome Cornfield. "Effect of Thyroidectomy and Food Intake on Oral and Intravenous Glucose Tolerances in Rats". Am. J. Physiology 179: 30, 1954

Soon, Robert O., and Jerome Cornfield. "Quantitative Relation between Oral and Intravenous Glucose Tolerance Curves". Am. J. Physiology. In press (1955)

Soon, Robert O., and Gayle K. Hogan. "Effect of Testosterone Propionate on Growth, Collagen, and Other Protein Fractions in Isolated Muscles of Thyroidectomized Male Guinea Pigs". Am. J. Physiology. In press (1955)

Soon, Norman F., and Robert O. Soon. "Hospital Complications in the Old Fellowship Conference Treatment of Thyrotoxicosis". [illegible]

Wolfson, G. H., and R. O. Soon. "Conversion of Thyroid Iodine, Administered and in vivo, to the Beta, Gamma and [illegible] Forms". J. Biol. Chem. In press (1955)

Wolfson, G. H., and R. O. Soon. "Depression of Rate of Beta-Iodine Concentration in Thyroid Gland and Serum by Single Injection of Thyrotropin". Endocrinology 55: 697, 1954.

Wolfson, G. H., and R. O. Soon. "Depression of Rate of Concentration Concentrations in Thyroid Gland and Serum by Single Iodine Concentration without Thyrotropin". Endocrinology 55: 697, 1954.

Wolfson, G. H., and R. O. Soon. "Effect of Various Fractions and of Iodine in Thyrotropin on the Rate of Radio-Iodide Concentration in the Thyroid Gland and Serum in Rats". Endocrinology. In press (1955)

Soon, R. O., and E. A. Kraay. "Effect on the Thyroid Gland of Experimental Alteration of the Level of Circulating Thyroxine in Rats with Subcutaneous Pituitaries". Endocrinology. In press (1955)

17. [illegible]

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Biochemistry and Physiology of Metabolism
SECTION

4. Bethesda
LOCATION

5. MRDD(Grip)-1
GRANT NUMBER

6. Nutritional significance of vitamin B_{12}, coenzymes, choline, and related compounds for the chick
PROJECT TITLE

7. Dr. H. A. Schaap Fox
PRINCIPAL INVESTIGATOR

8. Dr. O. N. Briggs; Linda M. Orth
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine the function, interrelationships, and requirement of these nutrients for optimal nutrition of the chick under various dietary conditions.

Methods Employed: A deficiency of each of these nutrients has been produced in dietary excision studies by use of a specific antagonist. The effect of various nutrients in relieving the deficiency of each inadequacy has been studied. The effect of these dietary alterations upon growth and histological alterations as well as chemical composition of certain tissues has been determined by usual laboratory methods.

Major Findings: (1) It has been shown previously in this laboratory that the severity of the vitamin B_{12} deficiency in young chicks could be markedly increased by inclusion of 20% fat in an otherwise adequate diet free of B_{12}. The percent of an added vitamin found in the composition of tissues, but with inadequate optimal growth promotion of B_{12}-deficient chicks fed the vitamin fat.

(2) The chick's requirement for B_{12} with the exception that 100 $\mu\mu g.$ $Co/kg.$ of diet, whereas optimal growth was obtained with 5 $\mu\mu g.$ $B_{12}/kg.$ of diet when no fat was added.

(3) In the absence of dietary B_{12} the concentration of B_{12} in the liver at 4 weeks of age was the same (10-50 $\mu\mu g./g.$ of tissue) with either 4 or 20% fat in the diet. The quantity of B_{12} in the liver

9. PHS-398 Research Plan - Continued

increased with dietary lead and was not affected by lead. In these high fat diets, therefore, an increase the dietary methionine content for B_{12} and not to affect absorption.

(4) The growth depression in the absence of B_{12} could be overcome by supplementary B_{12}, methionine, or the combination of the two plus 0.2% choline (not by either alone). Histologic skin lesions present at B_{12} deficient levels did not alter B_{12} concentration in the liver.

(5) The total fat and phospholipid concentrations in the livers were normal in the B_{12}-deficient chicks.

(6) Addition of choline (the exact minimum of methionine in a complete synthetic-type diet caused growth depression, hemorrhage and fatty infiltration of the liver of young chicks.

(7) The adverse effects of aflatoxin could be overcome with supplementary methionine, but not with choline or with a combination of the increased methionine and choline. Choline had a protective effect.

Significance to NIAMD Research: Aflatoxin would interact with [illegible] to increase the incidence of [illegible]. This is also true in other studies using the chick and may be of importance to man. The chick appears to be particularly well suited to the study of [illegible] B_{12}, the nutrient involved in methionine synthesis and

Personnel Changes of Project: No personnel changes have occurred during the past year. The [illegible] anticipated [illegible] associated with additional research [illegible] personnel.

10. STAFF-YEARS
OVERALL NUMBER

11. BUDGET DATA:

	ESTIMATED OBLIGATIONS	PERMANENT POSITIONS			MAN YEARS			OVERTIME (Dollars)
		GS&E	Others	Total	GS&E	Others	Total	
FY 1955	23,600	5/6	1	1 5/6	5/6	1	1 5/6	
FY 1956	26,600	1	1	2	1	1	2	

12. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
SERVICE & SUPPORT	☐	SERVICE ASSISTANCE	☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE OR OTHER AGENCIES OF THE FEDERAL GOVERNMENT, INCLUDING FIELD FACILITIES, OR CONSULTED ON THIS PROJECT; (GIVE 1955 OR 1956 IF DESIGNATION MUST BE WITHIN THE CURRENT BUDGET YEAR.)

Laboratory of Pathology, NCI-
Activities and Biometrics Branch, NIH, PHS-Cancer Chemotherapy

14. IF THIS PROJECT DESCRIBES, OR FORMS, OR PERHAPS BECOMES, PART OF A PROGRAM IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH PROGRAM. (IN SERIAL FORM, IF GIVEN ETC.)

None

15. [illegible]
[illegible]

16. List publications cited in this report. Abstracts from [illegible] 1954:

Spivey, M. H., J. H. Bragg, and L. G. Grebe. Effect of dietary [illegible] protein on vitamin B12 deficiency in nonregenerative anemia. Proc. Soc. Exp. Biol. Med. 85: 650 (1954).

17. List names and dates of research carried on this project during the year 1954:

None.

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Biochemistry and Physiology of Metabolism
SECTION

4. Bethesda, Md.
LOCATION

5. NIAMD- 60219-8
GRANT NUMBER

6. Studies on the metabolism of the chick and the mouse.
PROJECT TITLE

7. Dr. C. H. Sniggs
PRINCIPAL INVESTIGATOR

8. Dr. M. E. Harvey Fox; Lidia Cetnik
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To gain more information of a fundamental nature on this and unidentified factors, fat, vitamin E, lecithin, and other nutrients in the nutrition of the chick and the mouse so that this information may be applied to and connected with the nutrition of other laboratory animals with eventual application to man.

Methods Employed: By the use of highly purified, semi-synthetic diets consisting of all known nutrients (such as casein, glucose, cellulose, corn oil, purified salt mixture, and vitamins) except the nutrient being studied, groups of very young animals are reared in wire-floored cages under standard controlled conditions of heat, light, water, etc. The effect of dietary variables is measured by measurement of weekly weight changes, food consumption, and by clinical and biochemical changes in the blood and the tissues. Approximately 15 different groups (about 100 animals) are started on experiment each week and are continued 4 to 8 weeks.

Major Findings: This past year a variety of sub-projects were continued or new ones in progress. Major findings include:

(1) The addition of relatively high levels of lecithin (5%) to a synthetic diet for the chick resulted in improved growth rates. The reason for this effect is being studied.

(2) From 5 to 10% of finely ground bentonite was inadvertently added to the synthetic diet of the chick. This impurity was prevented by the injection of, or feeding of, high levels of vitamin A.

9. Project Description - continued

(3) The oxidic substance as such as it accumulates in the culture medium is most useful without signs of toxicity.

(4) When an amino acid mixture containing known requirements of all amino acids is given to the chick, growth is very poor. Additional studies indicated that the chick requires an unidentified factor(s) in order for growth.

(5) Dietary fat or fatty acids may not be required by the chick. In a number of experiments growth of chicks fed diets devoid of fat or fatty acids was equal to control chicks given fat. An experiment for dietary effects is now near when the fat was removed from the diet.

(6) In studies with folic acid deficiency in the chick a number of compounds related to pteroylglutamic acid were fed and the availability of the vitamin in overcoming a deficiency was studied. Aminopterin acid had a definite sparing action and had no effect in other deficiencies studied including pantothenic acid and choline acid.

(7) Great variation was found for an unidentified growth promoting factor in egg yolk and liver.

(8) A semi-synthetic diet containing all known growth factors has been developed for the study that results in normal growth and development when fed by the hand or by self-feeding only 6-8 grams. The diet has been found to be modified for metabolic experiments and is adequate.

Significance to ARSD Research: The project provides basic information essential to the complete understanding of nutritional and biochemical relationships in metabolism and disease.

Proposed Course of Project: Research this next year will be devoted to the investigation of still unidentified factors for the chick and the swine. Wherever possible, properties of each factor will be studied. Combined studies will be made to determine any interrelationships of folic acid, ascorbic acid, pantothenic acid, other vitamins, fat, amino acids, and minerals. Physiology studies with one animal will be combined with other animals.

10. USAID-6233-3-8
CENTRAL BUREAU

11. BUDGET DATA:

	ESTIMATED APPROPRIATIONS	DIRECTOR'S POSITIONS FROM	OTHER	TOTAL	USDH STAFF FROM	OTHER	TOTAL	FOREIGN NATIONAL
FY 1955	$1,300	5/6	3	3 5/6	5/6	2 2/3	3 1/2	
FY 1956	$5,300	1	3	4	1	3	4	

12. ACTION REQUESTED:

DESIGNATE	☒	ACKNOWLEDGE	☐
REVIEW & APPROVE	☐	CONSULTATION	☐

13. INDICATE THE CONTRIBUTING EFFECT OF THE PUBLIC HEALTH ACTIVITY ON OVERALL ECONOMIC DEVELOPMENT (NATIONAL PROVIDING SCHOOL FACILITIES, OR PERSONNEL FOR SCHOOL PROGRAMS, ETC. DURING 1955 OR 1956). IF NON-OPERATING UNIT SO STATE AND INDICATE SOURCE OF $.

None

14. ☐ WHAT PROJECT CHANGES, IMPLICATIONS, OR PROBLEMS ARISING FROM DEVELOPMENTS IN THE PUBLIC HEALTH SERVICE (OTHER ACTIVITIES OR PERSONNEL, APPROPRIATIONS OR FUNDS), THEREFOR HAVE OCCURRED (BY SERIAL No.)? (IF NOTHING SAY)

None

Patents, awards, and publications issued

15. AFMDC 6211.9
Serial Order

16. Most publications other than abstracts and theses appear in 1954.

Briggs, G. M. Recent advances in protein nutrition. Proc. 1st Conference Feed Conference, Cincinnati, Ohio, March 10, 1954. 10 pp.

Briggs, G. M. Major contributions to tables 2, 3, 4, 5, 6, and 7 and contributions to tables 45 and 50 in "Standard Values in Nutrition and Metabolism" edited by R. A. Clinton, Wright Air Development Center, Technical Report 54-484, pages 7-17, 72, and 155-160, 1954.

Briggs, G. M., and F. G. Hall. Performance and metabolism, assessment, pathology, and requirements of animals. Part of chapter for the textbook edited by Sewell and Morris, Iowaiana Press, 1954. pages 439-480, 501-504 and 525-527.

17. List by name and title of personnel awarded an Air Force degree during 1954.

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Biochemistry and Physiology of Reproduction
BRANCH

4. Bethesda
LOCATION

5. 8141-05-01 M.S.
GRANT NUMBER

6. Nutritional Studies with the Guinea Pig
PROJECT TITLE

7. Dr. Mary S. Reid
PRINCIPAL INVESTIGATOR

8. Dr. O. N. Briggs; Lilia O. Ortiz
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine (a) optimum effects (level and interrelation) of different nutrients, (b) the quantitative requirements of these nutrients, (c) by study their physiological action and interrelation with other nutrients, (d) to discover possible subclinical conditions and (e) reasons for frequently unfavorable action of such deficiencies.

Methods Employed: Guinea pigs at 2 to 3 days of age, weighing approximately 100 g. were placed on a purified diet supplied to all those nutritional factors except the one under investigation. To study the requirement for a nutrient, the ration used was supplied in graded amounts of the nutrient were added to the diet of different groups of animals. The lowest level which gave the maximum growth was considered to be the approximate level required.

Major Findings: 1. Choline studies.

(1) Choline deficiency was produced in the guinea pig for the first time. Definitive symptoms included growth failure, retention of nitrogen, lowered hematocrit and hemoglobin values, small cardiac hypertrophy and adrenal hemorrhages but no cardiac blood hemorrhages and no marked fatty infiltration of the liver. In a chronic type of deficiency some of the animals succumbed suddenly, apparently as a result of circulation failure.

(2) Requirement: 2.0 to 1.5 g./kg. of diet.

5. Project Description - continued

(3) Substitution compounds: Neither betaine nor methionine (important in the fat) produced any benefit when added to diets lacking choline but both supplemented adequate levels of choline. Diethylaminoethanol was equal to choline. When methionine and betaine were fed together, they were as effective as a corresponding level of choline. The guinea pig apparently requires a dietary supply of both moieties of the choline molecule to screen its metabolic requirements.

B. Fat studies:

(1) Fat deficiency was produced in the guinea pig for the first time. Deficiency symptoms: retarded growth, dermatitis, skin ulcers and loss of hair - could be overcome with corn oil or linoleic acid.

(2) Requirement: Some growth occurred with intakes of 1 to 15% dermatitis developed on low fat levels. Hydrogenated lard (containing no unsaturated fatty acids) produced better growth than the fat-free basal diet. There is still some question as to whether the guinea pig requires only unsaturated fatty acids or fat as such or both.

(3) Linolenic acid: When 20 mg./day were fed, growth was less than on 15 gms. corn oil (similar amounts of linoleic acid/day).

C. Vitamin A studies: Severe vitamin A deficiency was produced. The onset was hastened by omitting preformed sources from the diet. Symptoms were severe conjunctivitis, dystrophy, slight fat infiltration of liver, enlargement in a few animals.

D. Amino acids: Addition of arginine to 20% casein diet produced growth equal to that on the 24% casein diet. Glycine and methionine had no effect.

E. Salts: The Briggs salt mixture (5% of diet) produced as good growth as any tested. Potassium acetate (2.5%) is needed in purified diets.

Significance to USAMD Research: A fuller knowledge of guinea pig nutrition is desirable because, with the exception of the monkey, this animal is in some respects more like man than any other experimental animal. Since, through our investigations, it has become possible to rear them easily on a purified diet, they can be used for

4. Dietary deficiencies - continued

(3) Substitution materials: Edible tubules and protozoa (Euplotes in the rat) produced no growth when added to diets lacking choline but both supplemented with optimal levels of choline. Dimethylaminoethanol was equal to choline. When methylaminoethanol and methionine were fed together, they were as satisfactory as a corresponding level of choline. The animal apparently requires a dietary supply of both methionine and choline materials to cover its metabolic requirements.

5. Fat studies:

(1) Fat deficiency was produced in the guinea pig for the first time. Deficiency symptoms: Retarded growth, dermatitis, scaly sloughing and loss of hair. A beard of wet cream color often oil or linoleic acid.

(2) Requirement: Near growth occurred with 1% levels of 5 to 15%; dermatitis developed on low fat levels. Interpreted lard (containing no unsaturated fatty acids) produced better growth than did low-fat level diets. There is still some question as to whether the guinea pig requires only unsaturated fatty acids or fat as such or both.

(3) Linoleic acid: When 30 mg./day were fed, growth was less than on 1% corn oil (taken as equal to 300 mg. linoleic acid/day).

6. Vitamin A studies: Severe vitamin A deficiency was produced. The onset was heralded by cellular proliferation around the eyes. Symptoms have always occurred by seventy, eighty day intervals of life, sometimes prior to a few animals.

8. Amino acids: Addition of arginine to the basal diet produced growth equal to that on the 18% casein diet. Glycine and methionine had no effect.

9. Salts: The Bragg's salt mixture (5% of diet) produced as good growth as any tested. Potassium sorbate supplement (2.5%) is needed in purified diets.

Significance to Wild Research: A fuller knowledge of guinea pig nutrition [illegible] desirable because, with the exception of the monkey, this animal is in some respects more like man as an experimental animal. Also, through our investigations it has been possible to rear them easily on a purified diet, they can be used in

9. PROJECT DESCRIPTION -- Continued

changing factors responsible for (1) abnormal uterine contractions such as occur in certain forms of eclampsia, (2) degeneration of tissues such as dystrophy of muscles as observed in chicken, vitamin E and pulmonary inflammation, (3) impairment in enzyme and hormone production such as the disorder exhibited in the thyroid of vitamin A-deficient animals, (4) inhibition in the production of red and white blood cells by substances in dietary vitamin B_{12}, B_{12} and folic acid, (5) the injurious effect upon the gastrointestinal tract caused by the lack of certain vitamins such as folic acid, as well as in many other problems.

Proposed Course of Project: The above studies will be extended to determine the requirement of the guinea pig for fats and essential fatty acids, for amino acids, and other nutrients. The interrelationships of vitamin C and folic acid, using the chemical ascorbigenic diet, will be studied. It is likely that some of the scorbutic scurvy symptoms are probably due to a double deficiency of vitamin C and folic acid.

10. NEAR-6201-5
SERIAL NUMBER

11. BUDGET DATA

	ESTIMATED EXPENDITURES	AUTHORIZED POSITIONS: PROF	OTHER	TOTAL	MAN-YEARS: PROF	OTHER	TOTAL	REMARKS
FY 1955	18,300	1 1/3	1 1/3	2 2/3	1 1/3	1 1/3	2 2/3	
FY 1956	25,300	1	3	4	1	3	4	

12. BUDGET ACTIVITY:

RESEARCH [X] DEVELOPMENT [ ]

DEVELOPMENT & APPROVAL [ ] OPERATIONAL SUPPORTING [ ]

13. IDENTIFY AND DESCRIBE BRIEFLY ANY OTHER PROJECTS SERVING THE SAME OR SIMILAR PURPOSES, PROVIDING FUNDS, FACILITIES, OR SERVICES FOR THIS PROJECT DURING FY 1955 OR 1956. IF CONTEMPLATED, STATE WHEN AND PROBABLE SOURCE.

Laboratory of Technology and Biochemistry, NIAID, NIH, $225,000 per year

14. IF THIS PROJECT RESEARCH, DEVELOPMENT, OR PRODUCTION EFFORT HAS BEEN CONTRACTED IN THE PUBLIC HEALTH SERVICE (WHETHER CONTRACTOR IS PUBLIC OR PRIVATE), INDICATE BELOW (OR ON SEPARATE SHEET) THE TOTAL $ VALUE OF EACH SUCH CONTRACT.

None.

[illegible]

15. [illegible]
[illegible]

16. [illegible] [illegible] [illegible]

N.I.H. - 1
December 1954

Analysis of ARS Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Biochemistry and Physiology of Aging
SECTION

4. Bethesda
LOCATION

5. (MRSM - 6211)-10
SERIAL NUMBER

6. Nutritional effects resulting from exposure of diets to ethylene oxide.
PROJECT TITLE

7. Dr. E.A. Harris, Dr. O. Michelsen
PRINCIPAL INVESTIGATORS

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To determine the nutritional changes resulting from the exposure of diets to ethylene oxide and related gases.

Methods Employed: Finely ground chick mix was exposed to known concentrations of gas for definite periods of time. After sterility, the diets to receive treatment (those of the rats) were stored at 0°C. in an atmosphere (room, chicken). Control groups of animals and diet were exposed also. Rats growth factors which the diet was fed to determine the factor(s) in which the breaks down in and deficient. Chemical and microbiological analyses are made on the exposed diets to see which metabolite are destroyed.

Major Findings: Exposure of purified and stock diets to ethylene oxide diets. [The exposure time and concentration of ethylene oxide were comparable to those used in the commercial sterilization of food products.] Treatment of each component of the purified diet showed that little or no damage was done to the vitamin. Chemical and microbiological analyses indicated that all of the thiamine and most of the riboflavin are destroyed when synthetic thiamine are suspended in starch and are exposed under similar conditions.

Preliminary studies show that enriched white flour exposed to ethylene oxide is changed nutritionally to approximately the same extent as the purified diet.

Significance to FDA's Research: Ethylene oxide is being used on a small scale for the sterilization of a few food products. It is being used to a greater extent in the sterilization of a variety of pharmaceutical products, especially those that cannot be subjected to heat sterilization.

The changed processed by ethylene oxide on the nutrient value is of interest from a physiological standpoint. The present data suggests that growth inhibitors are formed when the vitamins are treated with ethylene oxide. It is too early to determine their potential value but one suggestion might be as pesticide for the control of mould's.

Proposed Course of Project: The immediate long-term objectives of the research will be studied and attempts will be made to determine the compounds formed as a result of ethylene oxide treatment. Studies may be extended to other foods since this material has produced effective results as a safe defense against any biological entities.

Budget Data Sheet

10. [illegible] 68113-10
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	PERMANENT POSITIONS			FTE YEARS			F.T.E. YEARS
		WASH	OTHER	TOTAL	WASH	OTHER	TOTAL	
FY 1955	17,700	1 1/3	1	2 1/3	2 1/3	1	2 1/3	
FY 1956	22,900	2	1 1/3	3 1/3	2	1 1/3	3 1/3	

12. BUDGET ACTIVITY:

NEW [illegible] ☒ [illegible]

[illegible] ☐ [illegible] ☐

13. [illegible] ANY SUBPROJECTS OF THE PROJECT [illegible], IF SUCH [illegible] STATIONS, PROVIDING TRAILS, PICNIC AREAS AND OTHER FACILITIES [illegible] 1955 or 1956? IF SUCH PLANS EXIST IN WHOLE OR IN PART, [illegible]

None

14. IF THIS PROJECT DOES INCLUDE OR PROVIDE FOR FACILITIES [illegible] OF THE PUBLIC PARK SECTION [illegible] FUNDS), EXPLAIN [illegible]

None

15. [illegible] - 4211.1-10
[illegible]

16. [illegible]

None

17. [illegible]

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Biochemistry and Physiology of Mineral Metabolism
SECTION

4. Bethesda
LOCALITY

5. NIAMD - Building 4
NEAREST MAILING ADDRESS

6. The nutritional requirements of the rumen
PROJECT TITLE

7. Dr. O. Kolenbrander
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine the nutritional requirements of rumen microorganisms for growth and fermentation.

Methods Employed: Rumen-ware and rumen ware for a variety of [illegible] various levels of fat and sodium. The presence of sodium, potassium, and calcium appeared to be critical and limited. Sodium, also was for a most particular element consist of sodium and/or potassium. The effect of sodium, the anion chloride, with the prevailing element was present of [illegible] as growth was concerned.

Major Findings: The action of supplemental sodium, potassium, and chloride in increasing growth and increasing turnover of [illegible] most of rumen is due to [illegible] by correcting an acidic condition in the rumen. However, this does not account for the entire action since [illegible] would there be [illegible] for [illegible] growth and [illegible].

When any of these elements were added as the chloride, not only was the growth promoting effect no longer apparent but the survival of the rumen was increased. Studies with rats receiving a purified diet containing [illegible] sodium and potassium confirmed the apparent toxicity of chloride.

Proposed Course of Project: Work has been halted pending the recruitment of a scientist to take over the project.

10. AID/A - 0211-33
SECRET (When Filled)

11. BUDGET DATA:

	GRANT AID TABLE I FUNDS	SUPPORTED ASSISTANCE			DA FUNDS			P.L. 480 TITLE
		GRANT	LOANS	TOTAL	GRANT	LOANS	TOTAL	
FY 1955	5,700	1/3	1/3	2/3	1/3	1/3	2/3	
FY 1956	5,700	1/3	1/3	2/3	1/3	1/3	2/3	

12. BUDGET CONTROL:

DESIRED ☒ ADVISABLE ☐

ESSENTIAL ☐ NOT ESSENTIAL ☐

13. IDENTIFY ANY UNCOMMITTED BALANCES OF THE FOREIGN AID APPROPRIATIONS, OR OTHER RESOURCES, PROVIDING FUNDS, + ASSETS, OR PROGRAMS FOR THIS COUNTRY IN CURRENT 1955 or 1956. IF CONSIDERED USEFUL BY AMBASSADOR SUBMIT SEPARATE MEMO TO (2)

None

14. IF THIS PROJECT CONTINUES, DO COMMITMENTS OF FUNDS & SUBSTANTIAL EXPENDITURES IN FUTURE YEARS ..... DO (Regular EXPENDITURES OF A CONTINUING NATURE), MODIFY ANY RESTRICTIONS (IF SO, EXPLAIN TO (2) IF CHANGE ASK):

None

15. NIAMD 60(B-1)
SERIAL NO.

16. LIST PUBLICATIONS ...
1954:

Wooley, Jerald G., and Olaf Mickelsen. Effect of pelvination, sodium ... caloline on the growth of young rabbits fed purified diets containing different levels of fat and protein. J. Nutrition 52: 591 (1954).

17. LIST HONORS ... AWARDS ...
... IN 1954:

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Metabolism
LABORATORY

3. Biochemistry and Physiology of Nutrition
SECTION

4. Bethesda
LOCATION

5. Niacin, Amino Acid and Protein Metabolism
SECTION TITLE

6. The nutritional requirements of the rabbit
PROJECT TITLE

7. Dr. C. Lindsleen
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT NARRATIVE

Objectives: To determine the nutritional requirements of the rabbit
[illegible] mineral interrelationship.

Methods & Progress: Three-week old rabbits were fed a purified diet containing varying levels of fat and casein. The significance of sodium, potassium, and calcium supplements to the diet was studied. Weanling rats were fed a diet containing similar amounts of sodium and/or potassium. The effect of varying the sodium concentration [illegible] the preceding elements was studied as growth was measured.

Major Findings: The ratio of supplemental sodium, potassium, and calcium in increasing growth and decreasing mortality of 3-5 week old rabbits fed purified diets was of significant importance by correcting an acidic condition in the animal. However, this does not account for the entire action since there were many cases where the urine pH was low while growth was good.

When any of these elements were added as the chlorides, not only was the growth promoting effect no longer apparent but the mortality of the rabbit was increased. Studies also [illegible] receiving a purified diet containing low but adequate levels of sodium and potassium confirmed the apparent toxicity of chlorides.

Proposed Course of Project: Work has been halted pending the recruitment of a scientist to take over the project.

10. [illegible] - 6[illegible]-11
[illegible]

11. [illegible]

	[illegible]	[illegible]			[illegible]			[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
FY 1955	$3,700	1/3	1/3	2/3	1/3	1/3	2/3	
FY 1956	$3,700	1/3	1/3	2/3	1/3	1/3	2/3	

12. [illegible]

[illegible] ☒ [illegible] ☐

[illegible] ☐ [illegible] ☐

13. [illegible]

[illegible]

14. [illegible]

[illegible]

15. [illegible]

16. [illegible]

Woolley, Donald G., and Olaf Mickelsen. Effect of potassium, sodium or calcium on the growth of young rabbits fed purified diets containing different levels of fat and protein. J. Nutrition 57: 521 (1955).

17. [illegible]

None

R.P.C. - 1

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Metabolism
LABORATORY

3. Biochemistry and Physiology of Nutrition
SECTION

4. Bethesda
LOCATION

5. NIAMD-Gc11-12
SERIAL NUMBER

6. Experimental obesity in animals
PROJECT TITLE

7. Dr. G. Mitchell
PRINCIPAL INVESTIGATOR

8.
8. Samuel H. Ershoshi
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine the biochemical and physiological disturbances that occur in animals during the development of obesity and the consequent loss of weight by obese animals.

Methods Employed: The rats are fed a high fat (65-70%) diet in which the animals gain weight that is appreciably below that of their controls. At intervals of experimental animals are killed, organs weighed and examined for gross pathology, carcass analyzed for protein, fat, moisture, and ash. Rats reaching a weight of approximately one kg. have been put on a variety of feeding regimens. In this phase of study is completed rats will be killed and carcass analyzed. Data and normal weight controls have been obtained on simulated high altitudes in order to study the effect of this variable on the physiological response of the obese rats.

Major Findings: The percentage of fat in the body of the rat related to feeding regimen is directly related to the body weight. The fat content increases from approximately 12% for 300 g. rats to 30% for 1200 g. rats. These values are for rats that were in weight equilibrium at that time of weighing.

There are suggestions from our earlier work that when weanling rats are put on the high fat diet they attain a higher final weight than when adult rats are started on the same diet. Controlled studies are under way which do not confirm that observation.

Reduction in body weight of obese rats was achieved by feeding restricted amounts of the high fat ration or unlimited amounts of a commercial stock diet. The weights attained at the end of the reduction regime were the same as those of normal adult rats.

9. Project Description - continued

especially of the young rats to consume high caloric density diets that may result not because the fat contributes pleasure as well as normal weight rats (with some rats Dr. Kittinger).

Four different strains of rats are started on the high fat diet the maximum weight attained varies with the strain. At the end of 25 weeks on the high fat diet, the AIR Sherman averaged 251 g, the Sprague-Dawley, 360 g., and the Osborne-Mendel, 555 g.

The pathological work done on the obese rats by Dr. Kittinger shows degeneration of the β-cells in the anterior pituitary and osteoarthritic lesions in the bones. The kidneys of many of the obese rats are 2 to 3 times the normal size, have many calculous deposits with dilated cortex and albumin plugs in the bladder. The testes and seminal vesicles are small with signs of interstitial tissue hyperplasia. The liver is enlarged both on an absolute and on a proportionate basis; in many cases the livers are fatty. The adrenals are slightly enlarged.

Significance to NIAMD Research: Obesity is listed as one of the major health problems today. The development of a means of producing obesity in experimental animals entirely by dietary means will permit the study of obesity in animals uncomplicated by major physiological changes. The primary aspects of this work will be on the changes that result from a reduction in body weight.

Proposed Course of Project: These rats will be carried on the present regimen until they have attained the weight of normal adult rats. They will then be studied to see if their physiological and metabolic functions are the same as those in animals that were never obese. These studies will include blood pressure measurements, body composition, reproductive capacity, incidence of disease, longevity, etc.

10. NIH-D-5011-28
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	ASSIGNED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	OTHER DATA
FY 1955	19,600	2/3	3 1/3	4	1/3	3 2/3	3 2/3	
FY 1956	23,600	2/3	4	4 2/3	1/3	4	4 1/3	

12. BUDGET ACTIVITY:

RESEARCH: [X] ADMINISTRATION: [ ]
REVIEW & APPROVAL: [ ] FINANCIAL ASSISTANCE: [ ]

13. IDENTIFY ANY COOPERATING UNITS IN THE PUBLIC HEALTH SERVICE OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN CURRENT 1955 OR 1956. IF COOPERATING UNIT IS WITHIN NIH CHECK(X) SERIAL NO.

Laboratory of Physical Biology, NIAMD-62129-07
Laboratory of Pathology and Biochemistry, NIAMD- 62125-07

14. IF THIS PROJECT DUPLICATES, COMPLEMENTS, OR PARALLELS RESEARCH BEING CONDUCTED IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH. (BY SERIAL NO.(S) IF WITHIN NIH)

None

Journals of the Pioneer Expedition

Personal Awards and Publications Record

15. [illegible]
Social Science

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS WHICH HAVE BEEN ISSUED DURING CALENDAR YEAR 1950:

Nickelsen, O. The addition of specific nutrients to foods. Public Health Reports 69: 975, 1954.

Carter, V. O., O. Nickelsen, and J. Lyp. The determination of [illegible]. J. Lab. and Clin. Med. 43: 469. 1955.

Taylor, J. L., A. Henschel, O. Nickelsen, and A. Keys. Some effects of [illegible] starvation with hard work on body weight, body fluids, and [illegible]. U.S.A.F. School of Aviation Medicine, Randolph Field Proj. No. [illegible] Report No. 5. 1955.

Carter, V. O., and O. Nickelsen. Factors Influencing the [illegible] methods for ketone and [illegible]. J. Agr. and Food Chem. 3: 1073, 1955.

17. LIST HONORS AND AWARDS TO [illegible] DURING CALENDAR YEAR 1955:

None

Research Grant Progress Report

Public Health Service

NIAID
INSTITUTE

3. Laboratory of Biochemistry and Nutrition
LABORATORY OR DIVISION

Biochemistry & Physiology of Nutrition
SECTION

4.
(Reserved for grant code number)

NIAID-02113-12
SERIAL NO.

Isolation of Factor 3 Induced Dietary Necrotic Liver Degeneration
PROJECT TITLE

K. Schwarz
PRINCIPAL INVESTIGATOR

OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: A new factor, designated Factor 3, was shown previously to prevent dietary necrotic liver degeneration. Factor 3 appears to be a new vitamin. The aim of the project is to isolate this new principle in order to identify it chemically and to have it available for clinical and nutritional studies.

Methods Employed: A fractionation procedure is tested and found to be easy and to reproducibly and successively developed further, which allows the concentration of Factor 3 from various natural source materials. Processes such as fractionated adsorption and elution, chromatography, solvent extraction, and precipitation with various agents, are applied. Special, new techniques are developed, which are particularly suitable for the purification of our unidentified substance.

All fractions and also numerous other natural products and chemical substances are tested in the prophylactic animal assay for activity in preventing dietary liver necrosis. Testing operations are performed, using routinely 250 male rat animals weekly. Weanling rats of the inbred Fisher strain are used.

Major Findings:

1. Screening natural source materials for Factor 3, forty different yeast samples have been tested to date. All Brewer's yeast samples are good sources

"primary growth" yields and Biskind yields are insufficient. Various human materials from Cedarcrofts are being assayed.

2. The purification process worked out for Factor 3 [it stops] permits routine production of my quantities of highly active material (50000 units per g). This corresponds to 95000 fold purification. Pilot plant operations have been reorganized, increasing the output of crude Factor 3 concentrate to twenty-five times. The laboratory process has been adjusted to the new, improved raw product, so that now larger quantities of highly purified Factor 3 become available. From coal fractions, a number of crystalline by-products have been isolated.

3. A short-term assay for Factor 3 has been developed using the Warburg technique measuring oxygen consumption of liver slices after chronic feeding of Factor 3. This is used routinely now for testing Factor 3 activity within 18 hours.

Significance to NIAID Research: Factor 3 appears to be a new vitamin. It may, if all turns an important role in intermediary metabolism and possibly afford new ways and means in treating diseases which hitherto were incurable, particularly fatal diseases of the liver.

Proposed Course of Project: The investigation of highly concentrated Factor 3 fractions has to be carried out further until, finally, the substance can be obtained in sufficient quantities in crystalline form. Subsequently, its chemical formula has to be established and ways of synthesis or large-scale preparation have to be developed.

HEARD-5211--2.1
SHEET NO.

BUDGET DATA:

	SALARY EXPENDITURES	BUDGETED POSITIONS			SALARIES			REMARKS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
T 1955	33,300	1 2/3	4	5 2/3	1 2/3	3 2/3	5 1/3	
T 1956	46,500	2 2/3	5	7 2/3	2 2/3	4	6 2/3	

BUDGET ACTIVITY:

[ ] Increase [X] Decrease [ ] Maintenance

[ ] Program & Expansion [ ] Program Maintenance

JUSTIFY ANY INCREASED NEEDS IN THE PROGRAM OUTLINE BELOW. IF CHANGES ARE MADE AMONG PROGRAM ITEMS, EXPLAIN IN DETAIL. IF INCREASES ARE NOT REQUESTED FOR 1955 OR 1956, THE CONSEQUENCES MUST BE EXPLAINED BELOW.

Section 20 Reconstruction and Conservation (Soil Conservation)

IF THIS BUREAU CONTRIBUTES, CONSULTS, OR COORDINATES RESEARCH OR SERVICES IN THE PUBLIC RELATIONS FIELD, EXPLAIN CONTRIBUTION OF BUREAU, INCLUDING PERSONNEL AND FUNDS INVOLVED.

NIAMD-02713-13
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

K. Schwarz. Introduction: Liver Necrosis Versus Fatty Liver and Cirrhosis, Ann. N. Y. Acad. Sci., 57: 6, 817 (1954).

K. Schwarz. Factors Protecting Against Dietary Necrotic Liver Degeneration, Ann. N. Y. Acad. Sci., 57: 6, 878 (1954).

K. Schwarz. Nutritional Liver Diseases Up-to-Date. The Merck Report, 63: 2, (1954).

LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Periodic Investigator Report

NIAMD
INSTITUTE

G. Laboratory of Biochemistry and Nutrition
LABORATORY OR BRANCH

Biochemistry and Physiology of Nutrition
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

NIAMD-02113 -14
SERIAL NO.

Studies on the Terminal Phase of Dietary Necrotic Liver Degeneration
PROJECT TITLE

W. Morris - Guest
PRINCIPAL INVESTIGATOR

OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: 1. To determine the cause and the nature of events leading to death from dietary necrotic liver degeneration in rats.

2. To assay different substances, especially vitamin E and thiamin, as to their therapeutic properties in the terminal phase of dietary necrotic liver degeneration.

Methods Employed: Rats dying from liver necrosis were weighed, sacrificed, autopsied, temperature, reflexes, blood glucose, appearance of the liver and the abdominal blood vessels were recorded. The response of blood glucose to intravenously and parenterally injected glucose was measured in both normal animals. Blood glucose concentrations in the portal vein of normal and dying animals were studied.

Animals dying from necrotic liver disease were given different treatments and the effect upon survival time and pathological features was recorded.

Major Findings: The immediate causes leading to death from dietary necrotic liver degeneration are severe hypoglycemia and vascular shock. Hypoglycemia develops a few hours before death. It is due to a defect in intestinal absorption since stomach and intestines are full of diet in dying animals and since glucose disappearance from the blood in such animals is normal. Portal blood glucose concentrations in such animals are occasionally normal even after oral administration of glucose.

The failure of glucose consumption can be favorably influenced by intraperitoneal injection of large amounts of insulin in GI animals. However, when they appear in the blood, the symptoms of hypoglycemia disappear and the animals survive for an average of 17 hours.

Significance to NIAMD Research:

Knowledge of the nature of the terminal phase of dietary necrotic liver degeneration is important because there seems to exist a certain relationship between the symptoms of this disease and liver diseases in the human. It is hoped that new methods can be developed for the treatment of the terminal phase of human liver injuries for which, up-to-date, no reasonable ways of treatment exist.

Proposed Course of Project: The effect of vitamin E and factor 3 on carbohydrate balance in sick animals will be studied further.

The role of vascular disturbances in the development of dietary necrotic liver degeneration will be more closely investigated, especially those of the portal system and of the circulation in the liver.

Therapeutic attempts will be continued with purified factor 3.

The failure of glucose absorption can be immediately influenced by intraperitoneal injection of large amounts of insulin (4 U. S. P.). Glucose that appears in the blood, the symptoms of hypoglycemia disappear and the animals survive for an average of 17 hours.

Significance to NIAMD Research:

Knowledge of the nature of the terminal phase of dietary necrotic liver degeneration is important because there seems to exist a certain relationship between the symptoms of this disease and liver diseases in the human. It is hoped that new methods can be developed for the treatment of the terminal phase of human liver injuries for which, up-to-date, no reasonable ways of treatment exist.

Proposed Course of Projects: The effect of vitamin E and factor 3 on carbohydrate balance in sick animals will be studied further.

The role of vascular disturbances in the development of dietary necrotic liver degeneration will be more closely investigated, especially changes of the portal system and of the circulation in the liver.

Therapeutic attempts will be continued with purified factor 3.

NIAMD-(8211-13)
SERIAL NO.

B. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	FOREIGN CURR
FY 1955	6,600		1 1/3	1 1/3		1 1/3	1 1/3	
FY 1956	6,600		1 1/3	1 1/3		1 1/3	1 1/3	

BUDGET ACTIVITY:

RESEARCH [X]

REVIEW & APPROVAL [ ]

C. IDENTIFY ANY COOPERATING UNITS OR PHS PUBLIC HEALTH SERVICE OR OTHER ORGANIZATIONS, INDIVIDUALS, FACILITIES, OR PERSONNEL FOR THIS PROJECT OR SUBPROJECT IN 1955 or 1956: IF COOPERATING UNIT IS PUBLIC USE ESTIMATED DOLLAR VALUE:

None

D. IF THIS PROJECT INVOLVES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT DUPLICATION OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

NIAMD-6211-14
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Project Description Sheet

NIAMD
Institute

Laboratory of Biochemistry and Genetics
LABORATORY OR BRANCH

Biochemistry & Physiology of Metabolism
SECTION

Section Chief Name Here
SECTION CHIEF

NIAMD-BBGMB-15
SERIAL NO.

The Metabolic Lesions of Dietary Necrotic Liver Degeneration
PROJECT TITLE

S. S. Chernick
PRINCIPAL INVESTIGATOR

OTHER INVESTIGATORS

PROJECT DESCRIPTION - Metabolic Lesions in Dietary Necrotic Liver Degeneration

Objectives: The objective of this project is to determine the mechanism of specific nitrogen diet provide and give rise to dietary necrotic liver degeneration.

Methods Employed: The metabolism of tissues, mainly of liver, of rats with dietary necrotic liver degeneration is examined by means of enzymatic studies on slices, homogenates or subcellular components under conditions designed to measure the integrated of various enzyme systems. Appropriate chemical procedures (manometric determinations, etc.) are employed to assay these abnormalities in specific enzymes.

Major Findings: In contrast to the events in other varieties of dietary liver, oxygen consumption of livers from rats and the homogenate also decline after a short period of incubation. Only liver shows this respiratory lesion. The change in metabolism is observed long before any histological manifestations of the disease appears. It is readily reversed by the choline supplementation or the animal of vitamin E or factor 3. Homogenates of deficient livers fortified with adenine nucleotides (ATP and ATP) respond in the normal manner. Coenzyme concentration studies have not provided clues as to the site of the lesion. Coenzyme A, while low in deficient livers, does not parallel the necrosis or respiratory decline.

Significance to NIAMD Research: Almost nothing is now known of the [illegible] biochemical events leading to cellular death in liver diseases. These studies delineating metabolic changes may reveal the most point to [illegible] metabolism and suggest therapeutic procedures. Further, since dietary necrosis liver degeneration is prevented by vitamin E, [illegible] an opportunity is offered to study the participation of these substances in liver metabolism.

Proposed Course of Project: The finding that metabolism is deficient in the alive but normal in the homogenate suggests that the procedure employed in maintaining the compartmentation of adenine nucleotides may be involved. During the next year we shall concentrate on these poorly understood mechanisms. A study of oxidative phosphorylation by mitochondria prepared from deficient and protected livers has been initiated. The problem of the participation and localization of vitamin E and factor 3 in cellular metabolism will continue.

NIAMD-4221-05
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PROGRESS REPORT
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	16,700	2	1	3	1 1/3	1	2 1/3	
FY 1956	17,700	2	1	3	1 1/3	1	2 1/3	

BUDGET ACTIVITY:

RESEARCH [X] DEVELOPMENT [ ]

DEVIATION APPROVAL [X] TECHNICAL ASSISTANCE [ ]

DESCRIBE ANY COORDINATING ROLE OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDED FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN SECOND 1955 OR 1956: IF COLLABORATION WITH NIH INTRAMURAL RESEARCH PROJECT [illegible]

IF THIS PROJECT REPRESENTS CONTINUATION OF PARASITIC RESEARCH NOW CARRIED IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF KNOWN HERE)

[illegible]

[illegible]

5 NBSIR-5913-15
REPORT NO.

6 [illegible]
1954.

7 [illegible]
YEAR 1954.

Form A-1
December 1966

Project description sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Metabolism
LABORATORY

3. Locusts
LOCATION

4. Endocrinology
SECTION

5. AM00 - 6211-15
SPECIAL NUMBER

6. The influence of the central nervous system on metabolism
PROJECT TITLE

7. Dr. Kathryn Knowlton
PRINCIPAL INVESTIGATORS

Dr. Evelyn Anderson

8. Mrs. Beatrice S. Miles [Deputy-Matter Shed]
OF ALL INVESTIGATORS

9. PROJECT I.D. IF KNOWN

Objective: To study the influence of the central nervous system on metabolism using dogs with neurosurgical lesions.

Methods Employed: Dogs are used for this study. Using aseptic operative techniques transections are made at the thoracic level and at various levels of the spinal cord. The animals are maintained at a constant ambient nature and given controlled diets. Determinations of nitrogen, sodium, and potassium balances, glucose tolerance and insulin sensitivity are made. The study is continued for 3 weeks before operation and as long as the animal survives postoperatively, which varies from one week to several months.

Major Findings: Following transection at the mid-thoracic level all of the dogs showed a decreased glucose tolerance, a definite retention of sodium, and increased urinary excretion of potassium, and a marked creatinuria. These changes lasted for a period of 2 to 3 weeks, except for the sodium retention, which disappeared after one week. The creatinine excretion usually went 25 to 50 percent on the day of operation and remained at that level. In some of the animals there was a negative nitrogen balance that lasted about 3 weeks. The resting blood levels of creatinine, nonprotein nitrogen, sodium and potassium remained consistently normal throughout the postoperative period. The stress of operation and the disturbed hormone pattern were not associated with any increased adrenal hormone in the urine.

Transection of the spinal cord between L-2 and L-3 was followed by a negative nitrogen balance, creatinuria, sodium retention, and increased excretion of potassium. These changes persisted for about 2 weeks postoperatively. The creatinine excretion returned to the normal level for about 2 weeks postoperatively and then gradually decreased as muscle wasting in the lower parts and extremities became apparent. The glucose tolerance was significantly increased. Adrenal hormone excretion in the urine was increased only on the day of the transection; otherwise it remained at the normal level. It was not increased following severely stressful surgery, such as laparotomy performed under anesthetic, or hemisuperficialization.

Significance to NICHD research: This is fundamental research underlying the problem of psychosomatic medicine and many other problems of clinical medicine. This is the first study reported in medical literature so far as I am informed.

Proposed Course of Project: This project is being expanded by three new projects:

(1) The influence of the central nervous system on the sodium and creatinine metabolism as used as transection of thoracic and spinal cord in dogs.

(2) The influence of the central nervous system on [illegible] activity, and on effects on the adrenal [illegible]

(3) The influence of the central nervous system on [illegible] renal function.

10. NIMD 6514-16
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	ADDITIONAL POSITIONS			ALL PERS			STAFFING INCR.
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	14,700	1	1	2	1	1	2	
FY 1956	14,700	1	1	2	1	1	2	

12. [illegible] ACTIVITY:

[illegible] APPROVAL ☐ CERTIFICATION ☐

STATUS OF APPROVAL ☐ [illegible] ☐

13. [illegible] activities related to [illegible], including [illegible] 1955 or 1956. If [illegible], [illegible]

Division of Neuropsychiatry, Army Medical Service Graduate School
Walter Reed Medical Center
Armed Forces Institute of Pathology

14. [illegible] PROJECT, [illegible] IN [illegible] PHASE). IDENTIFY [illegible]

None

15. NIMH - 6211(-16
SCIRA (M)(SS

16. LIST PUBLICATIONS WITHIN PAST 2 YEARS IF NOT LISTED ABOVE:
1954:

The Influence of the central nervous system on [illegible] and hormonal
Activity as Based on Irradiations of the Brain Stem in Dogs.
Evelyn Anderson, Kathryn Knowlton, Jillian T. Spence, Carl Heimann,
Gert A. Laqueur, Davis Mck. Bronson, and Walt Haymaker.
(Accepted for publication by Acta neuroveg[illegible]ativa, Vienna.)

Disorders of the Hypothalamus and the Pituitary Gland - Chap. 21
E. Anderson and W. Haymaker (Clinical Neurology. Ed. by A.B. Baker.
New York, Hoeber, 1955

17. LIST BOOKS AND CHAPTERS IF [illegible] PUBLISHED DURING
PERIOD 1954:

None

R.P.G. - 1
December 1958

Analysis of all Grants available

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition 3. Endocrinology
LABORATORY SECTION

4. Bethesda 5. NIAMD-60115-17
LOCATION SERIAL NUMBER

6. Studies on the physiology of ACTH and hypothalamus
PROJECT TITLE

7. Dr. Robert Guillemin
PRINCIPAL INVESTIGATOR

8. Dr. Bert L. Lequeux Jr., Andr[illegible] (Guest-Harvard) Jr. and [illegible]
(Guest-Univ. of Wayne)

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to further investigate the physiology of ACTH with respect to the neurohumoral control governing ACTH secretion and the effects of prolonged ACTH stimulation upon the organism.

Methods Employed: Transplantable ACTH-producing tumors have been used as a source of endogenous ACTH in Lit-L rats. The rapid development of tumor-induced hyperadrenal cortisism has been followed by studies of urine, sodium, potassium, nitrogen balance, urinary creatine and creatinine excretion, blood glucose, eosinophil leucocytes, and uterine cycling.

Major Findings: By the methods described hyperadrenal cortisism may be produced in the rats. This is characterized by hypertrophy of the adrenal glands, obesity, susceptibility to infection, glucosuria, lymphopenia, interruption of uterine cycling, marked increase in water turnover, moderate increase in the excretion of sodium, potassium, urinary creatine and creatinine.

Significance to NIAMD Research: Previously only ACTH derived from other species could be administered to rats to produce hyperfunctioning adrenal cortices. The interpretation of the results in such studies were necessarily complicated by questions of species differences and the possible development of immune antibodies. The availability of the ACTH-producing tumor-bearing rats has now made it possible to study the effects of continuous endogenous ACTH stimulation, under laboratory conditions without the complication of antibody formation.

10. STAND - 60115-21
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	CONTRACT POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	FUNDING SOURCE
FY 1955	$700	1		1	2/3		2/3	
FY 1956	$900	1		1	1		1	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] SERVICE & ASSISTANCE [ ]

13. IDENTIFY ANY COORDINATING UNITS OF THE SURGEON GENERAL, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, INVOLVED IN THIS PROJECT, OR CONSULTED ON THIS PROJECT DURING FY 1955 or 1956: IF COORDINATING UNIT IS OTHER THAN DIVISION OF RADIOLOGICAL HEALTH

None

14. IF THIS PROJECT IS RELATED, COMPLEMENTARY, OR PARALLEL TO ANOTHER PROJECT IN THE PUBLIC HEALTH SERVICE (INCLUDING NIH), GIVE BRIEF TITLE(S) OF OTHER PROJECT(S), AND BRIEF NOTE DESCRIBING THE RELATIONSHIP

None

15. NIAMD - 6216-17
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS THAT WERE PUBLISHED DURING CALENDAR YEAR 1954:

Neurosecretory Pathways between the Hypothalamic Paraventricular Nucleus and the Neurohypophysis. G.L. Lapeyre - J. Comp. Neurology 101: 1-12, 1954.

17. LIST HONORS AND AWARDS TO PERSONNEL ASSIGNED TO THIS LABORATORY DURING CALENDAR YEAR 1954:

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Endocrinology
SECTION

4. Bethesda
LOCATION

5. NIAMD - 6211-18
GENERAL NUMBER

6. Isolation, chemistry and bioassy of anterior pituitary hormones
PROJECT TITLE

7. Dr. Robert W. Bates, Dr. Peter Condliffe
PRINCIPAL INVESTIGATORS

8. Mr. Tulane Howard, Miss Alice Lackey, Dr. Jacob Furth (Guest-Harvard Univ.)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To isolate the anterior pituitary hormones (thyrotropin, corticotropin, growth hormone, gonadotrophins, and prolactin) and to elucidate their chemical composition. To acquire purified hormones (obtained from pituitary glands and blood obtained from slaughterhouse beef pituitary tumors).

Methods Employed: Hormones are made of pituitary glands and of human pituitary tumors. These materials are fractionated and studied by salt fractionation, solvent fractionation, isoelectric precipitation, preparative electrophoresis, chromatography and countercurrent distribution. Identification and quantitative estimation of the amino acid constitution of purified fractions are made by paper chromatography after hydrolysis with or without formation of volatile derivatives. The potency of all fractions must be determined by bioassay. Using iodine depletion in the chick thyroid for thyrotrophin, thyroxine using iodine depletion of the thyroid of the rat for thyrotrophin; corpora weight increase in pigeons for prolactin; seminal vesicle weight increase in rat for luteinizing hormone; uterine or ovarian weight increase in rat for follicle stimulating hormone and body weight increase in the rat for growth hormone.

Major Findings: The thyrotrophic hormone has been studied chiefly in the chick and a reliable method has been evolved for the bioassy of thyrotrophin using the one day old chick. It has been found that fasting of the animals during the entire period of the test and also the presence of a high level of iodine in the thyroid are necessary conditions for a satisfactory assay.

Preliminary results on fractionation of thyrotrophin were obtained. Human pituitary glands were found to contain approximately five times as much thyrotrophin per unit weight as the pituitary glands of sheep, cattle, or hogs.

There is some evidence that a method for bioassay of adrenocorticotrophin using normal rats instead of hypophysectomized rats may prove reliable.

Significance to NIAMD Research: The mechanism of action of the pituitary hormones is not, as yet, understood. Progress in this field depends upon an increased understanding of the chemistry of the hormones. To accomplish this end, it is necessary to isolate in a chemically pure state and to characterize these hormones. It is known that the pituitary secretes six hormones and it is important to determine whether others also exist.

Proposed course of project: The rate of progress in the isolation of the hormones is directly related to the availability of satisfactory methods of bioassay. Considerable effort must be continuously expended to maintain and develop more accurate, sensitive, rapid and specific methods of bioassay. The method of identifying amino acid constitution involved in studies on the structure of insulin and subsequently applied to studies on vasopressin and adrenocorticotrophin will be applied to thyrotrophin and growth hormone. Search for additional pituitary hormones will be maintained.

P.H.S. - 5
December 1955

10. NIAMD - 6211k-18
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	ALLOCATED POSITIONS			ALL STAFF			PROJECT DATE
		PHS	OTHER	TOTAL	PHS	OTHER	TOTAL	
FY 1955	30,700	2 2/3	1	3 2/3	2 2/3	1	3 2/3	
FY 1956	30,700	2 2/3	1	3 2/3	2 2/3	1	3 2/3	

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1955 or 1956. IF COOPERATING UNIT IS OTHER THAN INTRAMURAL RO (1):

None

14. IF THIS PROJECT RESULTED, OR APPEARS TO HAVE POTENTIAL FOR RESULTING IN THE PUBLIC HEALTH SERVICE (WITHOUT DUPLICATION OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH (BY SERIAL NO. (5) OF OTHER PHS

None

R.P.R. - 7
Document 1954.

Honors, Awards, and Publications Form

15. NIAMD - 62114-13
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN THOSE LISTED UNDER PUBLICATIONS DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATIVE TO THEIR RESEARCH DURING CALENDAR YEAR 1954:

None

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
Institute

2. Biochemistry and Nutrition
LABORATORY

3. Endocrinology
SECTION

4. Bethesda
LOCATION

5. [illegible]-2111-39
GRANT NUMBER

6. Assay of Insulin in Blood.
PROJECT TITLE

7. Dr. Evelyn Anderson; Dr. Robert Bolze
PRINCIPAL INVESTIGATORS

8. Mrs. Frances W. Franco; Joseph Ono (Guest)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to devise a method for the assay of minute amounts of insulin which would be applicable for the assay of insulin in blood.

Methods Employed: The alloxan diabetic hypophysectomized mouse is used. The fall in blood sugar in response to an intravenous injection of insulin is used as the measurement of response. The technical difficulties of collecting blood samples in the presence of vasoconstriction due to an intravenous injection of insulin and of determining blood sugar using amounts of blood as low as [illegible] are some of the problems which arise in developing a successful assay method.

Major Findings: Amounts of insulin as low as 100 microunits can be injected. (1 microunit is one millionth of a unit which is used to measure insulin.) Considerable gains have been made in an effort to bring the lambda value for the assay into a satisfactory range, but more work is still needed.

Significance to NIAMD Research: A satisfactory method for the assay of insulin in blood would prove a useful tool in the study of problems in carbohydrate metabolism and in diabetes.

Proposed Course of Project: To take steps to increase the sensitivity and accuracy of the method and to apply the final method to the assay of insulin in the blood of patients.

R.S.C. — 1.
December 1954

10. NEARO-6211A-10
SERIAL NUMBER

11. BUDGET DATA

	ESTIMATED EXPENDITURES	REQUIRED POSITIONS			FAE YEARS			PERCENT
		FAE	OTHER	TOTAL	FAE	OTHER	TOTAL	
FY 1955	13,300	5/6	1½	2 1/3	5/6	1½	2 1/3	
FY 1956	13,300	5/6	1½	2 1/3	5/6	1½	2 1/3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

DEVELOPMENT ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1955 or 1956: IF COORDINATING UNIT IS OTHER THAN ENTER-ED ABOVE PO(S).

Office of Biometry, NIAMD.

14. IF THIS PROJECT RESULTED, DURING THE PREVIOUS BUDGET YEAR, IN NEW PUBLIC HEALTH SERVICE (WITHIN DEPARTMENT OR PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

Annual Report of NBS Research Activities

(Research, Testing, and Publications Items)

15. NBSIR-5211.-19
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN REPORTS THAT HAVE BEEN PUBLISHED DURING CALENDAR YEAR 1951:

None.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS SUBJECT DURING CALENDAR YEAR 1951:

None.

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Endocrinology
SECTION

4. Bethesda
LOCATION

5. NIAMD - Bldg. 10
ROOM NUMBER

6. The influence of the central nervous system on creatine and creatinine metabolism as based on transection of midbrain and spinal cord in dogs.
PROJECT TITLE

7. Dr. Kathryn Knowlton
PRINCIPAL INVESTIGATOR

8. Mr. Leonard H. Tedia
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To study the role of the central nervous system in creatine and creatinine metabolism and the mechanisms by which its effects are produced.

Methods Employed: Dogs are used for this study. Using aseptic operative technique transections are made at the midbrain level and at various levels of the spinal cord. The animals are maintained at a constant food intake before and after operation. Determinations of creatine and creatinine in urines of dogs subjected to transection of the central nervous system by midbrain and various cord levels. Antigens of urinary constituents for [illegible] serum before administration to each dogs of glycine and creatine labeled with N^{15}.

Major Findings: Immediately after midbrain transection, creatinine excretion usually dropped permanently, while a predominance of creatine regardless was seen for a limited time only. After spinal cord transection there was a similar creatinuria. Creatinine excretion did not change immediately, but gradually declined later to a stable lower level.

Significance to NIAMD Research: Since creatine phosphate occupies a place of more importance in intracellular energy interchanges of the mammalian body, and since several hormones (e. g. androgens, estrogens, adrenocortical steroids) alter their

9. PROJECT DESCRIPTION — Continued

pituitary collagenase) are known to affect arteriosclerosis; however, further knowledge of factors and mechanisms of the system involved will contribute greatly to our understanding of arteriosclerotic disorders.

Proposed Course of Project: The conversion of P^{35} in urinary creatine and creatinine after feeding glycine labeled with P^{35} will be followed in dogs subjected to midbrain transection to permit more complete interpretation of the effects of midbrain damage on the metabolic course of these substances. Also, since the P^{35} content of other urinary nitrogenous constituents, information should be gained regarding other factors in the effect of the central nervous system on nitrogen metabolism.

Creatine labeled with P^{35} in the glycine moiety will be synthesized and fed, in order to label body creatine before spinal cord transection. Determination of the P^{35} content in urinary creatine and creatinine in such animals should result in direct knowledge of the course of the creatinuria following cord transection. Syntheses of P^{35} in muscle creatine and creatinine will also be determined.

It is also contemplated that limited studies of the modification of creatine metabolism by hormone administration or withdrawal will be of value.

N.T.O. - 2
December 1955

10. MIAMI = GRILLO-40
SERIAL NUMBER

11. SCHOOL DATA:

	APPROVED ENROLLMENT	ENROLLED PERSONNEL			DAY CARE			REMARKS
		PUPIL	TEACHER	SCHOOL	PUPIL	TEACHER	SCHOOL	
FY 1955	15,400	3	4½	3	3	6½	3	
FY 1956	15,400	3	3 1/3	3	3	6½	3	

12. SCHOOL ACTIVITIES:

CHECK ☐ ☐

13. [illegible] FOR THE FISCAL YEAR ENDING [illegible], IN EACH OF THE CATEGORIES, PARTICIPATING FUNDS, ADDITIONS, OR REDUCTIONS FOR SUCH PURPOSES IN FISCAL YEAR 1955 OR 1956: [illegible]

Contrast on Intermediate Periodical Grade - Grill-15

20. IF THIS PROJECT ASSEMBLES, CONSTRUCTS, OR REMODELS BUILDINGS, [illegible] IF THE PUBLIC SHARES EQUALLY WITHOUT DISCRIMINATION IN PROVISION, PARTICIPATION IN FUNDS, OR ACTIVITY WHICH [illegible]

None

15. NIMH - M211j-20
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN LITERATURE WHICH THIS PROJECT DURING CALENDAR YEAR 1953:

See project: Influence of the CNS on Metabolism, NIMH-M211j-16.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1953:

None.

1. National Institute of Industrial Psychology
London W.1.

2. Manchester and Salford
Universities

3. Manchester
University

4. Leicester
University

5. Trade - Unionist
Labour Leader

6. The Influence of the Central Training System on Early Occupational Success
Edward Glass

7. Dr. Edward De Bono (Cantab - Oxford University)
Medical Practitioner

8. Mr. Derek Bell (Lincoln - Oxford University), Dr. [illegible] (Oxford
Oxford Ph.D.), Mr. Clifford T. Morgan (Cornell - Johns Hopkins
Universities)
Other Psychologists

9. Edward Glass Test

Objectives: To study the psychological factors influencing success in
the selection and training of apprentices and the relative
importance of these factors in the different
occupations to which
(1) To test certain hypotheses about the nature and relative influence of the
of different mental, intellectual (verbal), psychomotor and
social or personal and moral factors.
(2) To investigate the relationship between these factors
and their importance for the general trend and development
patterns in boys following different occupations.

Methods: Boys are chosen for investigation when starting a training course
and then re-examined periodically during the course and after
completion. Data are fully tape-recorded, coded and punched.
Investigations to date have been concerned with the use of several
group intelligence tests, measurements of personal traits
(by means of inventories and questionnaires), and measures of
psychomotor and intellectual skill in occupational training, and
practising sessions. Following a suitable testing period, boys may
be requested either to add-on or repeat some of the tests.
Tests are continued during the post-training period for a group of
leaver controls. After each period a questionnaire designed to
obtain social attitudes is also completed by the boys themselves.

Major Findings: The studies have not yet progressed to enable any
definite findings to be reported.

but rather a general reduction in the overall renal plasma flow [illegible] glomerular filtration rate. Only one dog has been explored in this [illegible] wherein transection had no effect on renal arterial pressure.

Significance to NIMH Research: The prolonged survival of dogs with [illegible] and cervical cord transections affords us an unusual opportunity to study the role of the central nervous system in the regulation of renal and cardiac function. Exactly what part the nervous system plays in the regulation of normal fluid balance, cardiac output, arterial pressure and renal function is not known at the present time. These studies bear directly on our desire to understand clearly the mechanism of [illegible] physiologic alterations in the above parameters occurring in patients with specific nervous, endocrine, cardiac and renal dysfunction.

Proposed Course of Project: It is intended to study a series of dogs with [illegible] wherein and spinal cord transection. The acute and chronic alterations in renal and cardiac function, along with changes in the fluid and electrolyte balance. Specifically we plan to study changes in the renal clearance of [illegible] glomerular filtration, renal plasma flow, cardiac output, arterial pressure, extracellular fluid space and blood volume, along with balance studies including nitrogen, fluid and electrolyte balance.

R.P.No. 1
December 1954

10. NIMD - 6211h-21

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	PROFESSIONAL PERSONNEL			OTHER PERSONNEL			PROJECT TIME
		PMS	OTHER	TOTAL	PMS	OTHER	TOTAL	
FY 1955	3,000	-	-	-	-	-	-	-
FY 1956	3,000	-	-	-	-	-	-	-

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATIVE WORK OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT DURING 1955 or 1956. IF COORDINATION WITH OTHER ORGANIZATIONS IS INDICATED, EXPLAIN:

A.F.I.P., Army Medical Service.
Harvard University School of Medicine.
Georgetown University School of Medicine.
Armed Forces Institute of Pathology.

14. IF THIS PROJECT DUPLICATES, COMPLEMENTS, OR PARALLELS RESEARCH BEING CONDUCTED BY THE PUBLIC HEALTH SERVICE (Without Reimbursement of Funds), IDENTIFY SUCH RESEARCH (By Grant No. (s) or Project Title)

None

Section - 2
Document Type

15. NIMSO - 6511A-61
SERIAL NUMBER

16. List [illegible] as of [illegible] 1954.

None

17. List names and values of [illegible] Year 1954.

None

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Metabolism
LABORATORY

3. Endocrinology
SECTION

4. Bethesda
LOCATION

5. NIAMD - 6C11-22
SERIAL NUMBER

6. The influence of the central nervous system on endocrine activity
PROJECT TITLE

7. Dr. Hildegard Nilson (Guest - Georgetown)
PRINCIPAL INVESTIGATOR

8. Dr. David McK. Rioch (Guest - Walter Reed), Dr. William T. Spence (Guest - Georgetown), , Dr. Suey Saturnin (Guest - Fellow, Bangkok, Siam), Dr. Jane Norris (Guest - Walter Reed), Miss Inez T. Marques (Guest - Howard University)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The influence of the central nervous system on endocrine activity, as based on transections of the midbrain and spinal cord.

Objectives: To develop methods adequate for the routine determination of adrenal cortical steroids and adrenal medullary hormones in the blood and urine of dogs. To apply these methods in serial assays before and after transections of the midbrain and spinal cord.

Methods Employed: For the adrenal steroids in blood plasma, a CCl4 chloroform extract is prepared which contains both free and conjugated steroids. These are then separated, the conjugates hydrolyzed, and assays performed on the combined free fractions. The corticosteroid assay involves a micro determination of 17-ketosteroids after oxidation with chromic acid, and determines both 17-deoxy corticosteroids and 17-ketosteroids. Procedures for glucose determinations on dog urine are now under study. Adrenalin and noradrenalin will be extracted from urine by the method of Goldenberg et al., separated by paper chromatography, and determined separately. Bioassays are being set up, and chemical assays are planned.

Major Findings: The results obtained since July 1, 1954, concern the study of

adrenal steroids in blood plasma. In human plasma most will have been found in the free state, about one fifth conjugated as glucosiduronates, and the remainder as acid hydrolysable conjugates. In dog serum the totals were lower, and there was a smaller proportion of free steroids.

Significance to NIAMD Research: The evaluation of adrenal cortical function in dogs (or humans) by means of steroid assays when only small alterations are expected, requires refined methods. It is hoped that our procedures will reveal variations in plasma levels following ENE operations, thus reflecting the effects on adrenal cortical function. Parallel analyses of adrenalin and noradrenalin should reflect the participation of the adrenal medullary hormones.

Proposed Course of the Project: It is planned to follow the total plasma steroid levels in dogs before and after transections of the midbrain and spinal cord. If alterations are found, it will be possible to extract larger volumes of plasma and determine which fraction has been affected. Chromatographic analyses of adrenal venous blood of both normal and operated dogs are also planned, in a further effort to detect alterations in adrenal cortical activity.

10. [illegible]

11. BUDGET DATA:

	CAP STATUS (EXPENDITURES)	SUBSIDY ESTIMATES			LOAN ASSETS			REPAYMENTS
		PUBLIC	PRIVATE	TOTAL	PUBLIC	PRIVATE	TOTAL	
FY 1955	3,000	-	-	-	-	-	-	-
FY 1956	3,000	-	-	-	-	-	-	-

12. BUDGET ACTIVITY:

RESEARCH ☒ — ADMINISTRATION ☐

DEVELOP & APPROVAL ☒ — TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER FEDERAL AGENCIES, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL YEAR 1955 or 1956. IF COOPERATING UNIT IS OTHER THAN INDICATE CENTRAL OR (2)

Walter Reed
Georgetown University
Drexel University
Foreign Operations Administration (FOA)

14. IF THIS PROJECT DUPLICATES, COMPLEMENTS, OR PARALLELS RESEARCH OR [illegible] IN THE PUBLIC HEALTH SERVICE (EXCEPT [illegible]) OR [illegible], FACILITIES OF FOREIGN), IDENTIFY SUCH RESEARCH. (SEE CHAPTER HD-15) N (WITH NOTE)

None

15. NBSAM - 6211h-32
SERIAL NUMBER

16. LIST PUBLICATIONS ISSUED THAT CONTAINED ONE OR MORE PAPERS DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONS AS RELATING TO NBS PROGRAM DURING CALENDAR YEAR 1954:

None

P-1 (b) —1
December 1961

Project Description Sheet

2. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Enzymes and Cellular Biochemistry
SECTION

4. Bethesda
LOCATION

5. NIAMD-61115-21
PROJECT NUMBER

6. The enzymatic transformation of carbohydrates and their derivatives
PROJECT TITLE

7. Dr. D. L. Purich
PRINCIPAL INVESTIGATOR

8. Miss P. L. Cuppielle
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To provide further information on the pathway of carbohydrate catabolism in order to define the role of these reactions and intermediates in the chemistry of the cell.

Methods Employed: Cell extracts supplied from suitable sources for individual reactions are studied in detail and reaction products isolated and identified. These products are then employed as substrates for succeeding steps.

Major Findings: The ketose sugar formed from sedoheptulose 7-phosphate by transaldolase reaction has been identified as predominantly D-glucose 6-phosphate. This is the first example identified of heptulose catabolism. This sugar participates in the further reactions, the products of which have been identified as sedoheptulose diphosphate and triose 3-phosphate. Sedoheptulose diphosphate is a new compound whose main function appears to be to act as a reservoir for the unusable erythrose ester.

Further studies with purified transaldolase have already been established that this enzyme will react with D-erythrose 4-phosphate as well as with ribulose 5-phosphate, the aldolase which has previously for the first time an example of a possible linkage from Embden-Meyerhof pathway.

An identical series of reactions involving transaldolase and transaldolase has been shown to account for certain pentose metabolic

9. Project Description - Continued

In animal tissues and in plants. In the former pentose phosphate is used for reaction with aldehydes, while in the latter it provides the primary CO2 acceptor in photosynthesis. A partial answer has already been found in dihydroxyacetone from which pentose phosphate and ultimately hexose diphosphate is the substrate for the aldolase reaction in which 2 moles of dihydroxyacetone and are produced.

Two new enzyme reactions involving hexose phosphate isomers have been found to participate in the biosynthesis of histidine. One of these represents a new type of transamination reaction in which the carboxyl group is replaced by a phosphate ester linkage. Like other transamination reactions, it requires pyridoxal phosphate.

Significance to NIAID Research: The existence of a mechanism for the conversion of hexose monophosphate to pentose phosphate which is common to green plants and animals suggests that these reactions are important in the basic economy of the cell. Knowledge of these reactions opens the way to an examination of their role in normal and diseased cells.

Proposed Course of Project: Further work is needed to determine the detailed mechanism of the aldolase and transketolase reactions. In particular the role of bivalent cations in the former reaction and the participation of coenzyme in the second reaction will be investigated. Further examples involving the new amino acyltransferase reaction will be sought. The new histidine and carbohydrate enzymes will be purified in order to determine the substrate and reaction mechanism.

Budget of the Federal Government

Project Data Sheet

10. NIAMD-6031-3
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	SALARIED POSITIONS PROF	SALARIED POSITIONS OTHER	SALARIED POSITIONS TOTAL	MAN YEARS PROF	MAN YEARS OTHER	MAN YEARS TOTAL	UNITED SAC
FY 1955	28,600	2	2	4	2	2	4	
FY 1956	34,000	3	2	5	3	2	5	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

SERVICE & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATION WITH OTHER UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER AGENCIES, INSTITUTIONS, FOUNDATIONS, PRIVATELY FUNDED, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL YEARS 1955 AND 1956. (IF COOPERATING UNIT IS WITHIN THE INTRAMURAL PROGRAM, GIVE SERIAL NO.)

B. Lowe - Postdoctoral Fellow of the Public Health Service, American Cancer Society, Inc., Institutional Essential Personnel, USPHS, Sep-Dec 1954
L. Weissbach - Postdoctoral Fellow, National Foundation for Infantile Paralysis
J. Marsili - Postdoctoral Fellow, American Cancer Society
P. Stumpf - Postdoctoral Fellow, USPHS
E. Hiatt, NIAMD- 6031A-03A
P. Burke, NIAMD- "

14. IF THIS PROJECT DUPLICATES, COMPLEMENTS, OR PARALLELS RESEARCH BEING PURSUED IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH. (GIVE SERIAL NO(S) IF WITHIN NIH)

Section on Intermediary Metabolism NIAMD - 6031F-37

15. NIAMD-69113-03
SERIAL NUMBER

16. LIST PUBLICATIONS (GIVE FULL ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954):

The Mechanism of Pentose Phosphate Conversion to Hexose Monophosphate by B. L. Horecker, Morio Ishii, Yaoi Kimura, and P. Z. Saprnistis. J.A.C.S. 207, No. 1, 393 (1954)

The Mechanism of Pentose Phosphate Conversion to Hexose Monophosphate. II. With Pea Leaf and Pea Root Preparations. By Morio Ishii and B. L. Horecker. J.B.C. 208, No. 2, 813 (1954).

Pentose Phosphate and CO_2 Fixation with Spinach extracts. By B. L. Horecker, P. Z. Saprnistis and M. L. Hanover. J.A.C.S., 76, 3511 (1954).

Discussion in Symposium. By B. L. Horecker, Proceedings Fifth Int. Cong. Biochem. 5th, No. 5, 711 (1954).

The Enzymatic Formation of Alkaline Hexosephate. By L. Heinbecker, P. Z. Saprnistis and B. L. Horecker. J.A.C.S., 76, 5071 (1954).

Tetrose Phosphate and Sedoheptulose Diphosphate Formation. By B. L. Horecker, P. Z. Saprnistis, E. Stahl and P. Mehler. J. Biol. Chem., In press.

Purification and Properties of Yeast Transaldolase. By B. L. Horecker and P. Z. Saprnistis. J. Biol. Chem., In press.

Carbohydrate Metabolism. By P. Z. Horecker and Alex L. Mehler. Ann. Rev. Review of Biochemistry (1954), in press.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATED TO THIS PROJECT DURING CALENDAR YEAR 1954:

Millebrand Award (1954), Washington Academy of Sciences - Dr. B. L. Horecker

1. National Institutes of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Enzyme and Cellular Biochemistry
SECTION

4. Bethesda
LOCATION

5. (NIAMD-62115-C4
SERIAL NUMBER

6. Studies on the structure and intermediary metabolism of nucleic acids and nucleotides
PROJECT TITLE

7. Dr. Leon A. Heppel
PRINCIPAL INVESTIGATOR

8. Russell J. Milano
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to discover pathways for the biosynthesis and breakdown of nucleic acids and smaller nucleotide units.

Methods Employed: With enzymes purified from suitable sources various biochemical and degradative reactions are carried out. The products are examined by means of paper chromatography, paper electrophoresis, chemical analysis and ion exchange column chromatography.

Major Findings: The first successful enzymatic synthesis of ribonucleic acid (or longer ribonucleotide) from small molecules such as nucleoside monophosphates, was demonstrated by us last year. Pancreatic ribonuclease and a xylene diethanol polymer the synthesis by an unknown mechanism. This work has been extended and other ribonucleases of different specificities have also been shown to possess synthetic ability.

Ribonuclease has not been purified from spleen and liver and shown to have exactly the same enzymatic properties as the pancreatic enzyme. Spleen phosphodiesterase has been further purified and characterized.

A new series of transphosphorylation reactions have been discovered. Two enzymes have been separated. One catalyzes a transphosphorylation between ATP and various nucleoside monophosphates. The other catalyzes a similar reaction between ADP and various

9. PROJECT DESCRIPTION - Continued

nucleoside triphosphates. These reactions are possible as a result of all the various triphosphates which are believed to be precursors in nucleic acid synthesis.

A new deaminase has been purified several hundred-fold from spleen which rapidly converts adenosine to inosine.

Significance to NIMH Research: It is expected that these studies will provide information on the mechanism of nucleotide incorporation into nucleic acid synthesis. These substances are basic to the economy of all cells, and their normal metabolic pathway must be understood before possible alterations in disease states can be investigated.

Proposed Course of Project: The role of cyclic nucleotides and other nucleotides in nucleic acid biosynthesis will be further investigated. Purification studies of nucleases and deaminases will be continued and their mechanism of action studied by use of ^{32}P and other methods. Transphosphorylation reactions will be studied in greater detail, as well as a new phosphatase discovered in the course of this work.

Budget Data Sheet

10. NIAMD-62116-3A
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	NUMBER POSITIONS			MAN YEARS			PROFESSIONAL
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	$4,300	2	2	4	2	1½	3½	
FY 1956	$7,200	2	3	5	2	2	4	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THESE PROJECTS IN FISCAL 1955 or 1956; IF COOPERATING UNIT IS NIMH, GIVE GRANTEE SERIAL NO.:

None

14. IF THIS PROJECT TERMINATED, OR EXPECTED, IN FISCAL 55 OR 56, INDICATE WHERE RESULTS WILL BE USED IN THE PUBLIC HEALTH SERVICE (WITHOUT DUPLICATION OF RESOURCES, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (IF SERIAL NO(S) IS GIVEN, SAY SO)

Studies by Dr. Mary E. Glover (NCI) on another spleen nuclease are complementary to one part of the above project. NCI-

15. (GRANT-CONTRACT-#)
SERIAL NUMBER

16. LIST PUBLICATIONS (OTHER THAN ABSTRACTS) FROM THIS PROJECT DURING CALENDAR YEAR 1954:

The action of some nucleases on simple esters of mononucleotides. J. N. Brown, L. A. Heppel and R. J. Hilmoe. J. Biol. Chem. 206, 1, 1954.

Nucleotides and Nucleosides. L. A. Heppel. Chapter in Chemical Pathways of Metabolism, Vol. 2, Editor D. M. Greenberg.

Transphosphorylation between nucleoside pyrophosphates and nucleoside triphosphates. M. L. Stevenson, L. A. Heppel and P. O. Ortiz. Arch. Biochem. Biophys., 52, 100, 1954.

A note on the structure of triphosphopyridine nucleotide. M. L. Stevenson, P. O. Whitfield and M. Stephen. J. of the Chem. Society (British).

Nucleotide exchange reactions catalyzed by ribonuclease and other phosphodiesterases. I. Synthesis and Interconversion studies between 2'- and 3'-nucleotides. M. L. Stevenson and P. O. Whitfield. J. of the Chem. Society (British). In press

The enzymic hydrolysis of ribonucleoside-2'(3')-phosphogen phosphates. P. O. Whitfield, L. A. Heppel and M. Stephen. J. of the Chem. Society (British) In press

Nucleotide exchange reactions catalyzed by ribonuclease and other phosphodiesterases. II. Synthesis of 2'-polynucleotides. L. A. Heppel, P. O. Whitfield and M. Stephen. J. of the Chem. Society (British) In press

17. LIST HONORS AND AWARDS TO PERSONS RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

10. -- 1

Project Description (cont.)

3.

4.

IMSD-62115-05

Studies on the Biosynthesis and Degradation of Nucleic

esse C. Rabinowitz

. Jr. Yakow, Jr.

ROJECT DESCRIPTION:

Objectives: The objective of this project is to determine biological mechanisms for the degradation and synthesis of nucleic

Methods Employed: With enzyme preparations from mixed and inoculated bacteria, products of nucleic metabolism are isolated and identified using, among paper chromatography, paper electrophoresis, and isotopic techniques. The components synthesized by a bacteriophage induced bacterial [illegible] are also investigated and the metabolic requirements of these [illegible] studies in growth experiments.

Major Findings: The major findings of this project during the past year have included the identification of two enzymes which are [illegible] (1) the characterization of deoxyribonucleic acid deoxynucleases in the degradation of nucleic; (2) the isolation of a nucleotide not [illegible] with any known compound from extracts of the mammalian pancreas gland, and (3) the observation that this enzyme organism can also [illegible] in place of adenine only if histidine is added to the medium.

Significance to Arthritis and Metabolic Disease Research: [illegible] and are expected to aid and other products of [illegible]

are involved in energy transfer reactions in the form of nucleotides, which are components of nucleic acids and are found in all living cells. The metabolism of purines is therefore of fundamental importance to all living organisms. Knowledge of the enzymatic reactions involved in their biosynthesis, however, is fragmentary. The metabolism of purines in mammalian systems and the identification of the enzymes involved has been a fruitful means of disclosing metabolic pathways and organic components previously unknown. The occurrence of similar pathways or compounds in other normal and diseased organisms should thus be greatly facilitated.

Proposed course of project: Problems which shall be investigated during the next calendar year include (1) the identification of the compounds and enzymatic reactions involved in the conversion of formylmethionine to formic acid and glycine; (2) the characterization of the nucleotide accumulated by the Neurospora mutant; and (3) and evaluation of the general occurrence and significance in other biological systems of the compounds which may be found in these studies.

D. AID/W-6211.6-65
REVISED NO.

1. BUDGET DATA:

	ESTIMATED EXPENDITURE	BUDGETED POSITIONS			MAN YEARS			BUDGET DATE
		PMAF	OTHER	TOTAL	PMAF	OTHER	TOTAL	
FY 1955	18,500	2	1	3	2	1	3	
FY 1956	13,000	2	1	3	2	1	3	

2. BUDGET ACTIVITIES:

CONCURRENCE [X] APPROVAL [ ]

REVIEW & APPROVAL [ ] CONDITIONAL APPROVAL [ ]

3. IDENTIFY ANY COORDINATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER FEDERAL AGENCIES, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL YEAR 1955 OR 1956; IF COORDINATION WITH US MISSION NOT REQUIRED, EXPLAIN WHY.

None

4. IF THIS PROJECT ASSEMBLES EQUIPMENT, OR PARALLELS RESOURCES NOW ELSEWHERE IN THE PUBLIC HEALTH SERVICE (PCS/AMC INTERCHANGE OF PERSONNEL, EXCESS PROPERTY, FUNDS), INDICATE SUCH RESOURCES. (SEE PARAGRAPH NO.(5) IN HANDBOOK)

None

.P.C. - 2

0. NEAID-6211-S
SERIAL NO.

1. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PROGRAM CODE
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	13,800	2	1	3	2	1	3	
FY 1956	13,800	2	1	3	2	1	3	

2. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

3. IDENTIFY ANY COOPERATING UNITS IN THE PUBLIC HEALTH SERVICE, AS OTHER ASSOCIATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1955 OR 1956. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S) (IDENTIFY)

None

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH BEING CONDUCTED IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

N.I.H.

Project Description Sheet

1. NIAMD
INSTITUTE

4. Biochemistry and Metabolism
LABORATORY OR DIVISION

2. Enzymes & Cellular Biochemistry
SECTION

5. [illegible]
LABORATORY CHIEF (OTHER PRINCIPAL SCIENTIST)

3. NIAMD-ORIG-26
SERIAL NO.

6. Metabolism and Biological Function of Uridine Nucleotides
PROJECT TITLE

7. H. K. Kalckar (Visiting Scientist)
PRINCIPAL INVESTIGATOR

8. E. Maxwell
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To follow the biosynthetic pathways by which active uridine nucleotides involved in glucose, galactose and glucuronic acid metabolism in the liver are formed. To study the function of this type of nucleotide for the formation of coupled glucosamides (glycol, phenols) and mucopolysaccharides. To perform studies to examine the metabolism of uridine diphosphate glucuronic compounds in muscle and in various microorganisms.

Methods Employed: Large scale isolation of uridine diphosphate glucose from yeast with the help and facilities provided by Dr. Sarasteen and the equipment available in the Section of Isolation and Fractionation. Column chromatography (Dowex-2 chloride), paper chromatography and extensive use of enzymatic ultraviolet spectrophotometric methods to study the course of reactions.

Major Findings: Drs. J. Strominger, E. Maxwell and I published during early September 1954 the studies on the biosynthesis of the so-called "active" glucuronic acid through collaboration with Dr. Julius Axelrod, Laboratory of Chemical Pharmacology, National Heart Institute. The major finding of the project dealing with glucuronic acid metabolism was the discovery and subsequent isolation of the hitherto unknown metabolic unique, uridine diphosphate glucose dehydrogenase (UDPG dehydrogenase) which in the presence of diphosphopyridine nucleotide (DPN) catalyzes the oxidation of UDPG to uridine diphospho

glucuronic acid (UDPGA). The latter substance has recently been recognized as being identical with the so-called 'active' glucuronic acid. We have lately in collaboration with Dr. K. Ishihara of NIAMD, succeeded in demonstrating that the enzymatic oxidation product of UDPG (reduced with DPN and the above mentioned enzyme) gave rise to a substance which proved to be UDPGA ('active' glucuronic acid) chemically as well as biologically. The isolated oxidation product in the presence of microsomes and uridine glucuronide acceptors such as phenols or tetrahydro corticoids (cf. Dr. Isselbacher's report) brought about a rapid and efficient formation of glucuronides of the latter compounds.

A research project dealing with the UDPG metabolism in microorganisms resulted in the observation that Hemophilus influenzae and para influenzae contain enzymes which catalyzes a degradation of UDPG quite different from that observed in mammalian tissues, yeast, E. coli and in nonpathogenic strains of Hemophilus. This project was greatly assisted by the help and experience of Dr. M. Pittman of the National Microbiological Institute. Valuable material was also kindly sent to us from Ludwig Lehmann, American Cyanamide.

The project on metabolism of uridine nucleotides in muscle was performed in collaboration with Dr. W. W. Kelley of the National Heart Institute. It was found that an enzyme of the contractile protein, myosin, catalyzes the dephosphorylation of uridine triphosphate (UTP) with a rate considerably higher than that of adenosine triphosphate (ATP) (cf. Dr. Kelley's report).

Significance to Research in Arthritis and Metabolic Diseases: The general biological importance of the uridine diphospho glycosyl compounds for the metabolism during growth (normal or pathological) and especially for the formation of the so-called mucopolysaccharides (hyaluronic acid, chondroitin, bacterial immune polysaccharides) is now increasingly recognized. The discovery of the UDPG-dehydrogenase closes the missing link in the enzymes describing the conversion of glucose or glycogen to glucuronides. The fact that a niacin nucleotide (DPN) is involved in the formation of active glucuronic acid poses several questions of nutritional significance. It is rather likely that diseases in which the mucopolysaccharides show pathological alterations are in a more or less direct way correlated with disturbances in the formation or metabolism of uridine diphosphate glucuronic acid.

Proposed Course of Project: We have planned a further study of the properties of UDP-glucose dehydrogenase, especially as to the nature of a recently observed enhancing effect of amino acids on the rate of oxidation. Synthesis of C^{14} labeled active glucuronic acid from C^{14} glycogen (or sucrose) and UTP is now feasible since all the step enzymes can be isolated. We hope to be able to continue our very fruitful collaboration with Dr. Isselbacher on the metabolism of hyaluronic acid and related substances.

P.E. [illegible]

[illegible]

[illegible]

0. HSMHD-6413(S-2)
SPECIAL NO.

1. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			[illegible]
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$6,800	2	2	4	2	1½	3½	
FY 1956	$9,800	2	3	5	2	3	5	

2. ANIMAL ACTIVITY:

RESEARCH [X] [illegible] [ ]

SERVICE & TRAINING [ ] [illegible] [ ]

3. IDENTIFY AND COORDINATING UNITS OF THE PUBLIC HEALTH SERVICE, OTHER FEDERAL AGENCIES, PROVIDING NAMES, ADDRESSES, AS APPROPRIATE, FOR EACH COOPERATING UNIT DURING 1955 OR 1956: IF NONCOOPERATION MUST BE NOTED, SO INDICATE.

Dr. Richard Ackermann, Postdoctoral Fellow - Am. Cancer Society, [illegible]

Dr. Edward M. Wheat - Postdoctoral Fellow - USPHS - Gen. Chemist [illegible]

Dr. Milton Axelrod, Lab. Clinical Pharmacology, NIMH [illegible]

Dr. N. Fleisher, National Blood Institute

Dr. E. M. Bailey, National Cancer Institute - USPHS - NIH [illegible]

Dr. G. Brandbacher, NIAMD - Arthritis and Rheumatism Branch [illegible]

Dr. Schwangar - Section on Pharm. and Exp. NIAMD-NIH, MD

4. IF FIELD PROJECT REQUIRED, DESCRIBE BRIEFLY, OR PARALLEL RESEARCH NOW CARRIED IN THE PUBLIC HEALTH SERVICE INVOLVING INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH. (BY SPECIAL NO.(S) IF WITHIN PHS).

None

Analytical Ultracentrifuge Laboratory

Vacancy, Inventory, and Publications Sheet

5. NIAMD-UC-115-36
GENERAL (...).

6. LIST PUBLICATIONS OTHER THAN ABSTRACTS THAT THIS PROJECT DURING CALENDAR YEAR 1954:

Metabolism of Uridinediphosphoglucose (UDPGlucose) in Hemophilus Influenzae I.
Herman M. Kalckar, Acta Chemica Scandinavica 8, 1105 (1954).

The Biological Synthesis and Function of Cellular Polynucleotides.
Herman M. Kalckar, Science 119, 879 (1954).

Enzymatic Oxidation of Uridine Diphosphate Glucose to Uridine Diphosphate Glucuronic Acid. J. L. Strominger, E. S. Maxwell, J. Axelrod and E. S. Maxwell. J. Am. Chem. Soc. 76, No. 23 (1954).

7. LIST AWARDS AND HONORS TO PERSONNEL ASSOCIATED WITH THIS PROJECT DURING CALENDAR YEAR 1954:

None

Page 1

Project Description Sheet

Author
Technician

Enzymes & Cellular Biochemistry
Section

Dr. [illegible]
Laboratory of Chemical [illegible]

NIAMD-DCBIS-87
Project No.

Carbohydrate Metabolism in the Spleen and X-irradiated Mice
Project Title

[illegible]
PRINCIPAL INVESTIGATOR(S)

Jean [illegible]
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: Studies were done to obtained a partial alternative to the previous proposal entitled "The X-irradiated Mouse Spleen". In order to evaluate these observations, a study of the metabolism of various glycogens by the mouse spleen was undertaken.

Previous Work: Spleen hexose phosphatase was isolated and shown previously and the products isolated by chromatography on Dowex-formate resin identified by color reactions and were found to be responsible for the formation of deoxyribonucleic derivatives.

Major Findings: D-glucose phosphate has been demonstrated as a non-intermediate in the metabolism of glucose phosphate. This was the first satisfactory identification of this sugar in plant tissue, although its presence has been reported in various bacterial systems. During study of the metabolism of the various phosphates has resulted in the tentative identification of a new nucleic, acetyl-2-aminosugar phosphate, the formation of which is apparently dependent upon the presence of normally small amounts of copper.

Significance to Research in Arthritis and Metabolic Diseases: It is expected that knowledge of these pathways will help contribute to an understanding of the pathological effects of X-radiation. These results may also be utilized in other pathological conditions.

NIAID-2211-03
Serial No.

Proposed Course of Project: The intermediates described will be isolated in pure form and metabolic pathways of blood sugar components studied. The conversion of the interconversions will be studied with emphasis upon participation of the enzyme systems involved and with attention to the role of renal and other factors.

Amendment of NIH Program Activities

Budget Data Sheet

0. NIAMD-62215-07
SERIAL NO.

1. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	15,200	1	1	2	1	1	2	
FY 1956	15,200	1	1	2	1	1	2	

2. BUDGET ACTIVITY:

RESEARCH [X] DEMONSTRATION [ ]

SERVICE & APPRAISAL [ ] TRAINING ASSISTANCE [ ]

3. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, CONTRIBUTING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL 1955 OR 1956. IF COOPERATING UNIT IS OTHER THAN PUBLIC HEALTH SERVICE, GIVE [illegible]

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH NOW CONDUCTED IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

5. NIAMD-C2345-02
SERIAL NO.

3. [illegible]

Formation of Xylulose Phosphate from Ribose Phosphate by Xylose Isomerase. Gilbert Ashwell and Jean Hickman, J.A.C.S., 76, 5389 (1954).

Xylose Effect Activity in Irradiated Mice Treated with Xylose Phosphate, W. Gobbs, V. Anderson, G. Ashwell, Am. J. Physiol., 178, 466 (1954).

7. [illegible]

P.I. - [illegible]

[illegible]

[illegible]

[

equipment and personnel at the large-scale laboratory, maintenance
problems at the isolation [illegible], can be undertaken and discussed
elsewhere.

Proposed course of project: Immediately for the sake of [illegible]
attempts are being expanded, [illegible] are pondered, experiment
procedures and possible [illegible] can be carried out. This will increase
the number of isolation studies in which the large-scale laboratory could
[illegible] of help.

0. NIAID-62116-28
SERIAL NO.

1. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PERSONNEL COST
FY 1955	11,300	1	1	2	2/3	1	1 2/3	
FY 1956	13,100	1	1	2	1	1	2	

2. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATIVE [ ]

REVIEW & APPROVAL [ ] CLERICAL & OTHER [ ]

3. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL 1955 OR 1956: IF COOPERATING UNIT IS WITHIN DHEW INDICATE SERIAL NO(S) IF KNOWN:

Laboratory of Chemistry of Natural Products NIH-411

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH NOW CONDUCTED IN THE PUBLIC HEALTH SERVICE (WITHOUT DUPLICATION OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN DHEW)

None

Project Description Sheet

1. INSTITUTE: NIAMD
2. LABORATORY OR BRANCH: Laboratory of Biochemistry and Nutrition
3. SECTION: Fractionation and Isolation
4. LOCATION (IF OTHER THAN BETHESDA):
5. PROJECT NUMBER: ZAL

6. PROJECT TITLE: Microbiological assays for vitamins and amino acids

7. PRINCIPAL INVESTIGATOR: M. Silverman

8. OTHER INVESTIGATORS: N. Salzman, E. Rosing and H. Gardiner

9. PROJECT DESCRIPTION:

Objective: The determination of the concentration of various vitamins and amino acids in a variety of materials, such as achromic and macrocytic anemia body tissues and excretory products, can be carried out by the use of microbiological assays. Under this project samples submitted by investigators in nutritional and allied projects are analyzed for their content of the specific vitamin or amino acid under study.

Methods employed: The use of microbiological assays for the determination of amino acid continues to be of major importance in the problem on folic acid.

Significance to Arthritis and Metabolic Research: These microbiological assay procedures are a very important tool for the measurement of the concentration of various cell constituents, i. e., amino acids and vitamins.

Proposed course of project: With the expansion of laboratory findings in clinical investigations, there will be an increasing use of these assays from clinical materials.

10. NIAMD-02116-29
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	SUGGESTED POSITIONS			MAN YEARS			PRESENT DATE
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	23,600	2	3	5	1 1/3	3	4 1/3	
FY 1956	36,300	2	4	6	2	3	5	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

SERVICE & APPROVAL ☐ TRAINING ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL 1955 OR 1956. IF COOPERATING UNIT IS OTHER THAN INDICATED UNDER 9(5) [illegible]

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

Reports, Awards, and Publications (Cont)

5. NIAID-(N)16-55
SERIAL NO.

6. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

7. LIST HONORS AND AWARDS TO PERSONNEL ASSOCIATED TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

Page No. 1

Assignment of Investigative Activities

Project Description Sheet

1. Biology
DIVISION

2. Laboratory of Biochemistry and Metabolism
LABORATORY OR BRANCH

Fractionation and Isolation
SECTION

4. _____
LOCATION (IF OTHER THAN BETHESDA)

5. Grant-in-aid
Dental

Studies on folic acid
PROJECT TITLE

M. Silverman and J. C. Keresztesy
PRINCIPAL INVESTIGATOR(S)

G. E. Foval
OTHER INVESTIGATOR(S)

PROJECT DESCRIPTION:

Studies on folic acid:
(a) Naturally-occurring forms of;
(b) Enzymatic degradation of chlorovorum factor;
(c) The urinary compounds associated with folic acid metabolism in the rat.

Objectives: Folic acid, a vitamin of the B complex, has been shown to be essential for normal animal growth. The lactobacillus and yeast (S. cerevisiae) systems which are commonly employed to assay folic acid activity in biological materials are relatively insensitive to certain folic acid derivatives. Recently, however, more sensitive assay methods have been developed which permit the detection of folic acid derivatives in the picogram range. By identifying the naturally-occurring forms of folic acid, it will be possible to obtain new and more sensitive assay methods for folic acid. The presence of folic acid derivatives which are unable to support normal growth, but which are capable of inhibiting the growth of certain microorganisms, may be of significance in certain pathological conditions. Similarly, the identification of the products associated with folic acid metabolism in the rat may, in the future, lead to a better understanding of some of the fundamental processes of mammalian cell growth.

Methods employed:

(a) The microbiologically-inactive form of folic acid in liver can be converted to the active citrovorum factor form by incubation with liver. The problem is now resolved into preparing suitable extracts of the microbiologically-inactive folic acid and fractionating such extracts to obtain the required substance in pure form.

(b) Fractionation of liver extract for the purification of the enzyme which converts citrovorum factor in the presence of L-glutamic acid to folic acid. Conventional protein fractionation methods.

(c) The isolation of the substance believed to be related to lactobacillus in the urine of rats on a folic acid deficient diet is continuing, using solvent and chromatogram techniques.

Major findings: A water soluble conjugate of the bound form of liver folic acid has been prepared. N-10 formyl folic acid has been definitely identified as one of the products obtained in the autolysis of liver.

The oxidative degradation by whole rat liver preparations of various forms of folic acid was found to be related in some unknown manner to the dietary history of the rat.

On the injection of folic acid to human subjects, a folic acid form was found to be excreted which has some of the properties of reduced N-10-formyl folic acid.

Significance to Scientific and Industrial Community: The isolation and identification of the various metabolites of folic acid will result in a better understanding of biochemistry of such specific diseases as some of the anemias and leukemias. The mechanisms by which folic acid derivatives influence the formation of fundamental components of all living cells, the purines, are being widely studied. This project is directed to discovering the bound forms of folic acid which in the body and how they are changed from inactive to active forms.

Proposed course of project: The following are the goals for the coming year.

(1) Further purification of glutamate-CO$_2$-splitting enzyme.
(2) Isolation of the reaction product from the above enzyme and chromatographic study of its chemistry.
(3) Continue isolation studies of the lactobacillus-like substance in folic acid-deficient rat urine.
(4) Factors in diets that alter the oxidative degradation of folic acid by the livers of rats fed these diets. Establish the enzymatic processes involved in these reactions. Isolate and determine chemistry of the reaction products.
(5) Isolation of the microbiologically inactive form of folic acid in liver.
(6) Study the relationships between the biosynthetic formation of and the naturally-occurring forms of folic acid.

...U.S. -

...Department of the Public Health Service

...(Report Control Symbol)

...NIAMD-GCTIS-30
...SERIAL NO.

1. BUDGET DATA:

	ESTIMATED EXPENDITURES	ESTIMATED POSITIONS			MAN YEARS			PW...
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	19,100	2	1	3	2	1	3	
FY 1956	19,100	2	1	3	2	1	3	

2. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] CONSULTAL ASSISTANCE [ ]

3. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL YEAR 1956: IF COOPERATING UNIT IS WITHIN HHS INDICATE SERIAL NO(S) (NIH-1)

None

4. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH AND SERVICES IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN HEW)

None

Antibiotics and Other Chemotherapeutic Agents

Tumors, Blood, and Hematological Agents

5. NIAMD-S2116-30
SERIAL NO.

6. LIST PUBLICATIONS (OTHER THAN ABSTRACTS) FROM THIS PROJECT DURING CALENDAR YEAR 1954.

Tables in "Standard Values in Nutrition and Metabolism" 1953 in Handbook of Biological Data, The National Research Council (Tables 230, 126-, 1A7; pages 231, 232, 240). Wilson Silverman.

Isolation of B^{12} Factor, Folic Acid. M. Silverman, J. C. Sauberlich, and O. J. Koval. J. Biol. Chem. 211, 53-61 (1954).

Excretion of a Histidine Metabolite by the Rat. M. Silverman, W. J. Darby and F. S. Daft. Proc. Soc. Exp. Biol. and Med. 87, 451 (1954).

Isoglutamine and the Growth of Lactobacillus Arabinosus. M. Silverman, C. V. Lowane and F. S. Daft. J. Biol. 65, 97-107 (1954).

Synthesis of a Histidine Metabolite. J. L. Seegmiller, M. Silverman, [illegible] and A. H. Mehler. J.A.C.S. - December, (1954).

7. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

Project Description Sheet

2. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

3. Biochemistry and Nutrition
LABORATORY

4. Bethesda
LOCATION

5. NIAMD-GRTLY-31
GRANTS NUMBER

6. Study of Glucuronic Acid Metabolism
PROJECT TITLE

7. Dr. J. L. Lazar
PRINCIPAL INVESTIGATOR

8. None.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to elucidate the reactions by which glucuronic acid is oxidized in mammalian tissues.

Methods Employed: The enzyme which catalyzes the initial reaction in the oxidation of glucuronic acid, namely, the reaction glucuronic acid → glucuronic acid-1-phosphate, is obtained in cell-free extracts and purified. The course of the reaction is followed by coupling the product with glucuronic acid-1-phosphate pyrophosphorylase and triphosphopyridine nucleotide, and spectrophotometrically observing the reduction of the latter material.

Major Findings: A reaction between glucuronic acid and adenosine triphosphate has been demonstrated in extracts of dog tissues and the corresponding enzyme has been partially purified. The glucidic product serves as a substrate for phosphoglucomutase; this observation indicates that glucuronic acid is phosphorylated in the 1-position by kidney extracts in the presence of adenosine triphosphate.

Significance to NIAMD Research: Although an enzyme which oxidizes glucuronic acid to glucuronic acid has been isolated from liver, it has been demonstrated that this reaction does not occur to a detectable extent in vivo. However, it has been known that glucuronic acid is metabolized by intact animals. The results of this study will reveal how a non-phosphorylated intermediate is related to the

Project Description

1. [illegible] Intermediate of Ascorbic Acid Metabolic Pathway
[illegible]

2. Biochemistry and Nutrition
[illegible]

3. Intermediary Metabolism
[illegible]

4. Bethesda
[illegible]

5. [illegible]

6. Study of Gluconic Acid Metabolism
[illegible]

7. Dr. [illegible]
[illegible]

8. None.
[illegible]

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to elucidate the [illegible] when gluconic acid is utilized in mammalian tissues.

Methods Employed: The enzyme which catalyzes the initial metabolic step in the utilization of gluconic acid, namely, the reaction gluconic acid + glucose acid-6-phosphate, is obtained in cell-free extracts and purified. The course of the reaction is followed by oxidizing the product with gluconic acid-6-phosphate dehydrogenase and triphosphopyridine nucleotide, and spectrophotometrically observing the reduction of the latter material.

Major Findings: A reaction between gluconic acid and adenosine triphosphate has been demonstrated in extracts of hog kidney and the corresponding enzyme has been partially purified. The reaction product serves as a substrate for phosphogluconic dehydrogenase; this observation indicates that gluconic acid is phosphorylated in the 6th position by kidney extracts in the presence of adenosine triphosphate.

Significance to NIAMD Research: Although an enzyme which oxidizes glucose to gluconic acid has been isolated from liver, it has been demonstrated that this reaction does not occur to a detectable extent in vivo. However, it has been shown that gluconic acid is metabolized by intact animals. The results of this study will reveal how a non-phosphorylated intermediate is geared to the

10. HEAD-6111(-2)
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	REQUESTED POSITIONS PROF	OTHER	ANNUAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT BEDS
FY 1955	10,600	1	1	2	1	5/6	1 5/6	
FY 1956	12,600	1	1	2	1	1	2	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN BOTH 1955 or 1956. IF COOPERATING UNIT IS WITHIN PHS INDICATE SERIAL NO(S)

None

14. IF THIS PROJECT ASSEMBLES, COMPILES/ETC, OR MAINTAINS RESEARCH DATA ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT EXPENDITURE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN PHS)

Section on Enzymes and Cellular Biochemistry (NIAMD - B235-2)

15. NIAMD-62.17-11
SERIAL NUMBER

16. LIST PUBLICATIONS ISSUED WHOLLY OR IN PART FROM THIS PROJECT DURING CALENDAR YEAR 1958:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1958:

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Intermediary Metabolism
SECTION

4. Bethesda
LOCATION

5. NIAMD - Bldg. 10
CENTRAL OFFICE

6. The Metabolism of Glucuronic Acid
PROJECT TITLE

7. Dr. F. Eisenberg, Jr.; Dr. J.B. Field
PRINCIPAL INVESTIGATORS

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to elucidate the metabolic pathways of formation and utilization of glucuronic acid in animals and man.

Methods Employed: C^{14}-labelled precursors of glucuronic acid are incubated with guinea pig liver sliced in the study of glucuronic acid formation. C^{14}-labeled glucuronic acid and glucuronolactone are administered to patients in the study of glucuronic acid conjugation and incorporation into polysaccharides. In all cases, labelled compounds are isolated and the relative position of isotope determined. From data so obtained, the metabolic pathways traversed by the labelled compounds are assumed.

Major Findings: In the study of glucuronic acid formation it has been found that the immediate precursor of glucuronic acid in the guinea pig is its normal component. In the study of glucuronic acid utilization it has been found that glucuronolactone-C^{14} administered orally to a human is not incorporated into urinary glucuronic.

Significance to NIAMD: In view of the wide distribution of glucuronic acid in connective tissue, a defect in the metabolism of this compound may in some way be associated with arthritis and other diseases of that tissue. By following the metabolic course of isotopes, some insight should be gained concerning the way in which the normal human handles glucuronic acid. Comparison of results so obtained with those acquired from the study of diseased individuals may provide a clue to the nature of the biochemical lesions involved

Proposed Course of Project: Recent studies in other laboratories have indicated that glucuronolactone is physiologically different from glucuronate, and that the two molecular species are [illegible] not easily interconvertible. The plan for the coming year is to continue the study of labeled glucuronolactone metabolism and to compare it with the fate of labeled glucuronate in normal and [illegible] states, both with respect to conjugation and incorporation into polysaccharides.

10. [illegible]

11. [illegible]

	[illegible]	[illegible]			[illegible]			[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
FY 1957	15,500	1	1 1/2	2 1/2	1	5/8	1 5/8	
FY 1958	16,500	1	1 1/2	2 1/2	1	1/4	1 1/4	

12. [illegible]

[illegible] ☐ [illegible] ☐

[illegible] ☐ [illegible] ☐

13. [illegible]

None

14. [illegible]

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Intermediary Metabolism
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62117-3
Social Security

6. Mechanism of Action of Enzymes. I. The Mechanism of Action of the Phosphohexose Isomerases.
PROJECT TITLE

7. Dr. Yale J. Topper
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to study enzyme systems with respect to the catalytic chemical mechanisms by which they effect transformations of their respective substrates.

Methods Employed: The isomerizations effected by the two phosphohexose isomerases are studied in two ways: 1) non-deuterio substrates are exposed to the biological catalysts in the presence of D_2O and the distribution of deuterium in the products is determined; 2) deuterated substrates are incubated and the redistribution of the isotope is then studied.

Major Findings: In a preliminary study of a phosphohexose isomerase isolated from rabbit muscle it has been found that in the conversion of fructose-6-phosphate into glucose-6-phosphate, one atom of bound deuterium is incorporated into the product when the reaction is carried out in D_2O. This indicates that, just as in the case of the corresponding alkali-catalyzed reaction, the enzymatic isomerization conversion of the two hexoses involves the intermediary formation of an enediol.

Significance to NIAMD: Phosphohexose interconversion is one of the principal steps in carbohydrate metabolism. It is felt that a more detailed understanding of this and other enzymatic reactions will aid in the approach to various metabolic diseases.

Proposed Course of Project: A second phosphohexose isomerase which [illegible] fructose-6-phosphate and mannose-6-phosphate has recently been prepared from rabbit muscle by H. Stein. The physicochemical differences in the relationship between the two isomerases and their corresponding substrates will be investigated during the next year.

10. NAME - 0211-13
SERIAL NUMBER

12. BUDGET DATA:

	DOLLAR EXPENDITURES	PROGRAM POSITIONS			MAN YEARS			PAY DAYS
		P.H.S.	OTHER	TOTAL	P.H.S.	OTHER	TOTAL	
FY 1955	23,300	1	1	2	1	5/6	1 5/6	
FY 1956	26,300	1	1	2	2	1	2	

12. BUDGET ACTIVITY:

RESEARCH ☒ M.C.H. INSTALLATION ☐

SERVICE ☐ RESEARCH ASSISTANCE ☐

13. IDENTIFY ANY CONSTRUCTION OF THE PUBLIC HEALTH SERVICE, OR OTHER FEDERAL AGENCIES, RECEIVING FUNDS, FACILITIES, OR PERSONNEL AS SET FORTH IN ITEM 1, DURING 1955 AND 1956: IF CONSTRUCTION WILL BE INVOLVED GIVE APPROXIMATE DOLLAR AMOUNT.

None

14. IF THIS PROJECT INVOLVES, OR INCLUDES, OR PROPOSES TO INCLUDE CONSTRUCTION IN THE PUBLIC HEALTH SERVICE (OTHER THAN USE OF PERSONNEL, FACILITIES, OR FUNDS), IDENTIFY SUCH CONSTRUCTION (OR SERIAL NO. (S) IF ITEM 10)

None

15. NIAMD - G2117-32
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
LABORATORY

3. Intermediary Metabolism
SECTION

4. Metabolic
LABORATORY

5. NIAMD - 62111-3
SUBJECT MATTER

6. Humoral Antagonists of Insulin
PROJECT TITLE

7. Dr. J.B. Field; Dr. D. Steiner, Jr.; Technician- Mr. J.J. Leith
PRINCIPAL INVESTIGATORS

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to determine whether the [illegible] of insulin-resistant diabetic patients contain an agent or agents which are responsible for the observed resistance. If so, a quantification and characterization of the resistance is desirable.

Methods Employed: The physiological activity of insulin is determined by noting the augmentation of glycogenesis produced in the isolated rat hemi-diaphragm in the presence of the hormone as compared to controls with no added insulin. Using data from such experiments on normals, the sera obtained from insulin-resistant patients will be assayed for an anti-insulin effect.

Major Findings: The method for assaying insulin activity, using incubated hemidiaphragms of Lyman-Leblond rats as a test system, has been investigated.

Significance to NIAMD: Establishment of the presence of an insulin antagonist, in the sera of insulin-resistant diabetics would certainly lead to a deeper understanding of this phenomenon, particularly during periods of acidosis and infection.

Proposed Course of Project: The first series of experiments will be concerned with the refinement of the method employed in assaying for insulin activity and in testing for the presence of humoral insulin antagonists. Use will then be invoked to attempt to fractionate appropriate [illegible] sera in order to purify and characterize the agent or agents.

Budget Data Sheet

10. NIAMD - 62117-24
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PROJECT DATES
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	12,000	1	2/3	1 2/3	5/6	2/3	1½	
FY 1956	16,000	1	1	2	1	1	2	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] PROFESSIONAL ASSISTANCE [ ]

13. IDENTIFY ANY ACCOUNTING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, AGENCIES OR FUNDS, FACILITIES, OR PERSONNEL FOR WORK PERFORMED IN FISCAL 1955 or 1956: IF COOPERATING UNIT IS OTHER THAN PUBLIC HEALTH SERVICE (S)

None

14. IF THIS PROJECT INVOLVES, CONTRACTS, OR AGREEMENTS WITH OTHER ORGANIZATIONS IN THE PUBLIC HEALTH SERVICE (WITHOUT EXCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH AGREEMENT: (BY SERIAL NO. (S) IF WITHIN NIH)

Section on Endocrinology NIAMD 62114-19

15. NASA - 6117-34
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN NEWSPAPERS FOR WHICH YOU HAVE WRITTEN DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS RECEIVED IN ADDITION TO THOSE PREVIOUSLY LISTED DURING CALENDAR YEAR 1954:

None

Attachment-2

Progress Report of Projects: 1) Some common & exclusive results will be discussed in the meeting. 2) The work proposed will be carried out in the simultaneously presence and absence of the magnetic field. 3) The same procedure will be repeated on suitable metal complexes. 4) Extended periodic and energy level charts will be studied in the next session.

10. NIAMD - 5011Y-35
SCIENTIFIC AREAS

11. BUDGET DATA

	ESTIMATED EXPENDITURES	REQUESTED PERSONNEL			ALL PERSONNEL			PERSONNEL CHANGE
		PHS	OTHER	TOTAL	PHS	OTHER	TOTAL	
FY 1955	16,000	2	2	4	1 1/3	1 1/6	2½	
FY 1956	22,300	2	2	4	2	2	4	

12. SUBJECT ACTIVITY

RESEARCH ☒ ADMINISTRATIVE ☐

REVIEW & APPROVAL ☐ TRAINING OR ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN 1955 or 1956. IF COOPERATING UNIT IS PHS, INDICATE SECTION, ETC.

None

14. IF THIS IS NOT TO BE A GRANT, DESCRIBE BRIEFLY THE PURPOSE, NATURE AND EXTENT OF SERVICE TO BE RENDERED TO OR FOR THE PUBLIC BY THIS PROJECT (WITHOUT EXTENSION OF PARAGRAPH, IF NECESSARY, USE SEPARATE SHEET). INDICATE EACH ORGANIZATION (BY SERIAL NO. (S) IF KNOWN) TO BE SERVED

Section on Endocrinology NIAMD 6221-06

Analysis of NIH Project Statistics

Awards, Awards, and Publications Sheet

15. NIMH - M2117-25
Serial Number

16. LIST PUBLICATIONS ONLY THAT RESULTED FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"The Origin of Urinary Creatine in Progressive Muscular Dystrophy", by J.D. Benedict, H.J. Kalinsky, L.A. Staurosa, A.A. Wertheim, and D. Stetten, Jr., J. Clin. Invest. (in press).

17. LIST HONORS AND AWARDS TO PERSONNEL ASSIGNED TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

Project Description (cont.)

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition 3. Intermediary Metabolism
LABORATORY SECTION

4. Bethesda 5. NIAMD-62117-06
LOCATION SERIAL NUMBER

6. Metabolism of Glycogen
PROJECT TITLE

7. Dr. W. R. Stetten; Dr. D. Stetten, Jr.
PRINCIPAL INVESTIGATORS

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To gain insight into the nature of the normal turnover of the glycogen of liver and muscle.

Methods Employed: Radioactive glucose is administered to animals and subsequently liver and muscle glycogen are isolated. The glycogen obtained is degraded enzymatically by methods designed to split off glucose residues in a systematic fashion and to yield a series of limit dextrins. The fragments are assayed for radioactivity.

Major Findings: Glycogen, although yielding only glucose on total hydrolysis, is metabolically inhomogeneous. Glycogen turnover does not consist merely of replacement of preexisting molecules by newly formed molecules. Instead, glucose residues are added to, and removed from, the nonreducing ends at the periphery of the polysaccharide molecule. By a continual process of branching, glucose residues find their way from the peripheral tiers into the more centrally located layers.

Significance to NIAMD Research: Alterations and defects in the way the body metabolizes various carbohydrates have been found to be characteristic of certain nutritional states, drug actions and metabolic diseases such as diabetes and Von Gierke's disease. Any additional knowledge as to how carbohydrates are normally handled may be expected to contribute to a better understanding of the nature of these conditions and diseases.

5. Publications (Give titles of publications resulting from this project during the past year.)

Proposed Course of Project: Correlation between the size of glycogen molecules and the quantity of glycogen found in livers and muscles after standard periods of fasting and after administration of certain hormones or drugs will be sought. In this study a method of molecular weight determination involving reaction of carbonyl groups with radioactive cyanide, suggested by Isbell, is being developed. The method may prove useful in the study of other polysaccharides.

P.H.S. -1
December 1955

Budget and Staff

10. NIAMD-60,117-06
SERIAL NUMBER

11. BUDGET DATA:

	RECOMMENDED EXPENDITURES	PROFESSIONAL POSITIONS: PRES	OTHER	TOTAL	MAN YEARS: PROF	OTHER	TOTAL	PERSONNEL DATE
FY 1955	23,900	1½	1½	3	1 1/3	2 2/3	3	
FY 1956	25,900	2	2	4	2	2	4	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY AND COORDINATE EFFS OF THE PUBLIC HEALTH SERVICE, AS OUTLINED [illegible] SATIONS, PROVIDING NAMES, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL 1955 or 1956; IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None

14. IF THIS PROJECT RESULTS, CONCLUSIONS, OR FINANCIAL ASSISTANCE WAS RECEIVED IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERACTIONS OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

15. NIMH-5211(-)6
SERIAL NUMBER

16. LIST PUBLICATIONS (MIMH) DERIVED FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"A Study of the Nature of Glycogen Regeneration in the Intact Animal", by M. R. Stetten, and D. Stetten, Jr., J. Biol. Chem. 207, 351 (1954).

"Glycogen Regeneration in Vivo", by M. R. Stetten and D. Stetten, Jr., J. Biol. Chem., (in press).

17. LIST AWARDS AND HONORS TO PERSONNEL RELATED TO THIS PROJECT DURING CALENDAR YEAR 1954:

Alvarenga Award of Philadelphia College of Physicians - M. R. Stetten, Jr.

Annual Report — Analysis of Continuous Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition 3. Intermediary Metabolism
LABORATORY SECTION

4. Bethesda 5. Z1AM-6211-3
LOCATION SERIAL NUMBER

6. Evaluation of Catabolic Pathways for Glucose in Intact Cells
PROJECT TITLE

7. Dr. S. Bloom; Dr. P Ellenberg, Jr.
PRINCIPAL INVESTIGATORS

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objectives of this project are: 1) the determination of the extent to which the glycolytic pathway operates in the catabolism of glucose in normal tissues; 2) a comparison of this quantity with the role of the glycolytic pathway in various pathological states.

Methods Employed: The methods employed to date have primarily involved determination of the radiochemical yield of carbon dioxide from various C^{14} labelled substrates in vitro and in vivo. Also, a specific technique for the analysis of radioactivities in carbons 1 and 6 of glucose has been developed.

Major Findings: It has been demonstrated that approximately 1/3 of glucose metabolism in liver slices derived from normal rats proceeds via the glycolytic pathway, and that the remaining 2/3 of glucose catabolism is consistent with the requirements of the oxidative pathway. It has also been shown that diaphragm sections obtained from normal rats catabolize glucose exclusively through the glycolytic pathway, although this tissue is capable of oxidizing glucose acid, a product of the oxidative pathway. Furthermore, it has been observed that in liver slices derived from diabetic and fasted rats an increased fraction of glucose is glycolyzed as compared to that catabolized non-glycolytically.

Significance to NIAMD Research: In order to properly evaluate the disturbances in glucose metabolism occurring in those pathological conditions characterized by abnormal carbohydrate metabolism, it is essential to understand the behavior of glucose in normal cells.

5. PROJECT DESCRIPTION - continued

The primary antigen in this system [illegible] candidate [illegible] candidates with vaccinating.

Proposed Course of Project: To date, work on this project has primarily involved the use of isolated liver and [illegible] such studies will be extended to other tissues such as brain, spleen, heart, testes, kidneys, etc. Also certain aspects of this problem will be pursued in vivo.

[illegible]

[illegible]

10. NIAMD-GELL-37
SERIAL NUMBER

11. PERSONNEL DATA:

	ESTIMATED EXPENDITURES	ALLOCATED POSITIONS			MAN YEARS			PROJECT DATE
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	16,900	1½	1 1/3	2 5/6	1 ½	1 1/3	2 5/6	
FY 1956	20,900	2	1⅓	3⅓	2	1⅓	3⅓	

12. PROJECT ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PARTICIPATING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL YEAR 1955 or 1956. IF COOPERATION MUST BE WITHIN THE LABORATORY GIVE SERIAL NO(S)

None

14. IF THIS PROJECT PARALLELS, COMPLEMENTS, OR DUPLICATES RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF GIVEN NIH).

Section on Enzymes and Cellular Metabolism

15. NIAMD 6C317-07
SECRET WORK

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"The Fraction of Glucose Catabolized via the Glycolytic Pathway", by S. Gluc and D. Totten, Jr., J. Biol. Chem., (In press).

17. LIST NAMES AND AWARDS TO PERSONS RELATED TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

1. National Institute of Arthritis and Metabolic Diseases

2. Chemistry
LABORATORY

3. Carbohydrates
SECTION

4. Bethesda
LOCATION

5. PHS- 6018-2
GRANT NUMBER

6. New Analgesic Agents Derived from Sulfation
PROJECT TITLE

7. Lyndon F. Small
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Continuation of studies on new derivatives derived from sulfation of morphinan and other hydroxyamine compounds.

By invitation of the Secretary General of United Nations Journal on Narcotics of three international reports on weight of opium, Geneva, Switzerland, N. Y.

Completed remaining portion of antinociceptive screening and biochemical studies.

Budget Data Sheet

10. NIAID- 62116-38
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PAYMENT DATE
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1957	15,700	1	1	2	1	1	2	
FY 1958	15,700	1	1	2	1	1	2	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN SECTIONS 1955 or 1956; IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None

14. IF THIS PROJECT ASSEMBLES, COMPILEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH. (BY SERIAL NO(S) IF WITHIN NIH)

None

15. NIAMD- 62110-38
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Lewis J. Sargent and Lyndon F. Small. Carbinolamines derived from 5- and 8-Acetyl-1,2,3,4-tetrahydroquinolines as Pharmacicides. J. Org. Chem. 19, 1400 (1954).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

Project Description Page

2. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

3. Laboratory of Physical Biology
LABORATORY OR BRANCH

5. Physiology
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD- 62129-39
SERIAL NO.

6. The effect of roentgen radiation on tissue growth and differentiation
PROJECT TITLE

7. Helen G. Park
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To study patterns of growth and differentiation in simple tissues after various doses of roentgen radiation.

Methods Employed: Hydra, a fresh water coelenterate, has been used in these studies because of its ability to regenerate (differentiate) lost parts and because during asexual reproduction growth (mitosis) can be relatively easily separated from differentiation (morphogenesis).

Major Findings: Three major findings of the past year have been: (1) Small $MgSO_4$ and glutathione together when added to an inorganic medium protect hydras against the regeneration-inhibiting effects of roentgen radiation. The protective effect is potentiative and not additive. It seems particularly significant that protective results when the two agents are given after irradiation. (2) That a dose of roentgen rays which is lethal to 72% of adult animals in 24 hours kills only 16% of their newly developed offspring. This difference in sensitivity apparently does not exist at sub-lethal doses when reproduction is used as a criterion. (3) That roentgen radiation is more effective in preventing the initiation of development than in interference with morphogenesis once development has started.

9. PROGRESS REPORT - (Continued)

Significance to NIAMD Research: These studies show that it is possible to separate radiation effects on growth and morphogenesis and partly, at least, to counteract radiation effects by chemical means. They also illustrate the use of a relatively simple, asexually reproducing animal to obtain information about factors that affect tissue growth in general.

Proposed course of project: (1) To study the time sequence in which [illegible] and DNA exert their effects. (2) To study the effect of single and repeated low doses of ionizing radiations on the course of tissue growth and differentiation. The direction of this project will be shifted gradually to problems of metabolism and growth.

R.F.C. - 1
Document Title: Analysis of AID program submission

Budget Data Sheet

10. NEA/S- 0212S-69
SPAIN RC.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			REMARKS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1968	6,100	1		1	1		1	
FY 1969	6,100	1		1	1		1	

12. BUDGET ACTIVITY:

REMARKS ☞ ADMINISTRATION ☐

REVIEW & APPROVAL ☞ TERMINAL ☞

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN [illegible] 1968 or 1969. IF COOPERATING UNIT IS WITHIN AID INDICATE SOURCE WITH [illegible]

None

14. IF THIS PROJECT RESPONDS, SUPPLEMENTS, OR MODIFIES ACTIVITIES [illegible] IN THE PUBLIC HEALTH SERVICE (WITHOUT INFORMATION OF FINANCING, MODALITIES, FOCUS), IDENTIFY SUCH RELATION: (BY SERIAL NO.(S) IF PREVIOUSLY)

None

P.H.S. - 6
December 1956

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIAMD 62129-39
SERIAL NO.

15. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Daniel, G. E. and G. D. Park. A protective effect of inorganic magnesium against X-ray damage to hydra. Am. J. Roentg., Radium Therapy & Nuclear Med., 72: (5) 857-866. Nov., 1954.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954.

None

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
Institute

2. Chemistry
Laboratory

3. Carbohydrates
Section

4. Bethesda
Location

5. NIAMD-
Serial Number

6. Higher carbon sugars, anhydro sugars, sugar alcohols and their derivatives
Project Title

7. R. K. Richtmyer
Principal Investigator

8. J. M. Orett, L. C. Stewart, I. Slaon
Other Investigators

9. Project Description

Objective: To evolve generalizations relating the physical properties of the groups of substances named in the project title to their configurations and conformations.

Recent Progress: The synthesis from D-xylose, by a combination of chemical and biochemical methods, of the new crystalline pentose, lyxulose, and hopefully, arabinose (both are only sugars with the alpha-, gluco-, ido-, and gulo-configurations but also those with the allo-, manno-, talo-, and probably the gala-configurations from D-erythro pentodialdose, are in self explanatory terms of substances that formed from D-xylose, 1-allo-heptitol, 2-deoxy-D-arabino-hexose, 3-D-gluco-heptulose, D-manno-heptulose, 2-D-arabino-heptitol, and a second anhydride from D-glycero-D-ido-heptitol, and synthesis of 1,5-anhydro-D-arabitol, and proof of structure of its anhydromannitol products of D-mannitol.

Current and Projected Investigations: Proof of structure of the new anhydro sugars and extension of the investigation to additional sugars; also extension of the studies to sugar alcohols and their anhydrides and acetals.

A.I.D. - 1
Revision [illegible]

62118-39

10. MIAMI-
[illegible]

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGET FOR FISCAL YEAR			FULL TERM			PLANNED BASE
		DOLS	OTHER	TOTAL	DOLS	OTHER	TOTAL	
FY 1955	38,600	4	2	6	4	2	6	
FY 1956	38,600	4	2	6	4	2	6	

12. BUDGET ACTIVITY:

[illegible] ☒ [illegible] ☐

[illegible] ☐ [illegible] ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER [illegible] PARTICIPATING, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1955 OR 1956. IF COOPERATING UNIT IS PUBLIC HEALTH SERVICE, [illegible]

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH BEING CONDUCTED IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES, OR FUNDS), IDENTIFY SUCH RESEARCH. (SEE SECTION 30(B) OF [illegible])

None

[illegible]

[illegible]

15. [illegible]
[illegible]

16. List publications other than journal articles that the author cited in the publication:

Emmanuel Hirsch and Roland K. Richtmyer. [illegible] and [illegible] of D-Arabitol (Synonym, D-Lyxitol). A [illegible] and [illegible] Symbol. J. Am. Chem. Soc., 76, 1618-1620 (1954).

Laura O. Stewart and Roland K. Richtmyer. The [illegible] and 2,6-Anhydro-5-glycero-D-D-galo-heptopyranoside from D-glycero-D-galo-Heptose in Acid Solution. J. Am. Chem. Soc. (In press).

Laura C. Stewart and Roland K. Richtmyer. Determination of D-Ribose as 2,6-Anhydro-D-D-galopyranose in Acid Solution. J. Am. Chem. Soc. [illegible]

James W. Scott and Roland K. Richtmyer. Preparation of D-Allose [illegible] Anhydro-D-D-Allopyranose in Acid Solution. J. Am. Chem. Soc. [illegible]

17. List papers and books in preparation including in each instance the probable publication date:

Roland K. Richtmyer elected Chairman of the Division of Carbohydrate Chemistry of the American Chemical Society, 1954.

1. National Institute of Arthritis and Metabolic Diseases
[illegible]

2. Chemistry
[illegible]

3. Carbohydrates
[illegible]

4. Peptides
[illegible]

5. [illegible]-6218-b0
[illegible]

6. Microanalytical Laboratory
Project Title

7. W. C. Alford
Principal Investigator

8. Mary Jane Barrett, guest, Ruth B. Fullaton, Evelyn V. Penn, Ruth Todd C. B. Ansbacher, and V. M. Jones
Other Investigators

9. Project Description

The microanalytical laboratory is a service organization which performs many necessary analytical services for research personnel of the National Institutes of Health. The scope of this work is summarized as follows:

1. From 5,000 to 10,000 elemental or functional group determinations are made annually. These include carbon, hydrogen, chlorine, sulfur, nitrogen, iodine, iodine, phosphorus, arsenic and various functional groups such as acetyl, active hydrogen, methoxyl, nitrosyl, etc. Because of this type of routinely provided for approximately 200 research workers of the NIH staff. In addition, analyses are performed for governmental agencies outside the NIH, insofar as they can be handled without jeopardizing the progress of the research. For example, during the past year several thousand analyses have been done for personnel of the Naval Medical Research Institute, Bethesda, Md., The Tuberculosis Research Laboratory, USPHS, New York, and the National Bureau of Standards. Other agencies which have at various times received needed services include: The Naval Research Laboratory, Anacostia, District; Workers at Camp Detrick, Md., Food and Drug Administration, Washington, D. C., and the Maryland State Health Department.

2. A laboratory operated by Mr. Irene Gaertner performs routine routine for the Carbohydrates Section of the Laboratory of Chemistry. This laboratory was established late in 1954 and is providing, at present, about 75 individual services per month. This number will undoubtedly be increased as conditions become stabilized.

3. The services of Mr. Ansbacher are available for routine micro and macro analyses. For example, during the past year he has made over 1,000 determinations of lactic acid and pyruvate for Dr. Du Vigneaud.

4. Immediate control is available to personnel having specific problems what the laboratory is now equipped to handle. For example, visitations have been instituted to Pennsylvania Bureau of Mines laboratories for taking large samples of water pollution analyses.

Significance to FWQA and Bldg: The work done by the aforementioned laboratory is of vital importance to many research scientists. The analyses aid in identifying unknown materials or poisons, preliminary oversee proof of purity and quantity of materials submitted, and provide information needed to follow the progress of various research programs. Satisfactory chemical analyses are required for publications before the synthesis of new compounds.

Proposed course of Project: It is contemplated that this service will be continued and updated in every way possible.

Exhib. A-2
December 1954

10. NIAID-6R11B-40
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	SUPPORTED POSITIONS: PERM	OTHER	TOTAL	MAN YEARS: PERM	OTHER	TOTAL	PAYMENT DATA
FY 1955	33,300	2	4	6	2	4	6	
FY 1956	33,300	2	4	6	2	4	6	

12. BUDGET ACTIVITY:

ARRANGED ☒ ADMINISTRATIVE ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. INDICATE THE COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL 1955 OR 1956: IF COOPERATING UNIT IS WITHIN THE LABORATORY SERVICE, SO STATE:

The National Cancer Institute has provided the salary of Dr. Mary Jane Barnett (GS-9) during the past year.

14. IF THIS PROJECT REPRESENTS, COMPLEMENTS, OR PARALLELS RESEARCH BEING CONDUCTED IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES, FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF STUDIES EXIST)

None

15. NIAMD- 62118-40
GRANT NUMBER

16. LIST PUBLICATIONS UNDER THIS AEGIS RESULTING FROM THIS PROJECT DURING CALENDAR YEAR 1954.

None

17. LIST DEGREES AND AWARDS TO PERSONNEL RESULTING IN THIS PROJECT DURING CALENDAR YEAR 1954.

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Carbohydrates
SECTION

4. Bethesda
LOCATION

5. ZIAAM- 6211.3-03
FISCAL NUMBER

6. Ribose Derivatives
PROJECT TITLE

7. H. G. Fletcher, Jr.
PRINCIPAL INVESTIGATOR

8. R. K. Ness
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To elucidate the chemistry of the sugar ribose with the object of developing methods for the synthesis of biologically important ribosides.

Methods Employed: Guided by the theory of the interactions of certain groups within molecules, a large variety of chemical reactions have been used.

Major Findings: Methods developed earlier in this project for the synthesis of nitropyranosides and nitrofuranosides from ribose diacetonides have, in our hands, led also to ribose orthoesters of unique structure. Because of the vital part played by ribose and its derivatives in living organisms it seemed worth while to expand our knowledge of ribose through investigation of these orthoesters. 1,2(3)-Isopropylidene-5-O-trityl-D-ribofuranose has been synthesized in crystalline form and shown to rearrange spontaneously into a substance which was proved to be 1,2,3-orthobenzoyl-α-D-ribopyranose.

Significance to NIAMD Research: Understanding of the chemistry of ribose has been increased.

Proposed Course of Project: The behavior of orthoacid derivatives of nitrofuranose will be studied further and the information thus gained applied in an investigation of the synthesis of a moiety of the DPN molecule, the so-called "nicotinamide riboside."

10. [illegible] 5010A-1

11. [illegible]

	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	21,000	14	8	34	24	7	31	
[illegible]	23,650	15	8	39	46	7	38	

12. [illegible]

[illegible] ☐ [illegible] ☐

[illegible] ☐ [illegible] ☐

13. [illegible] [illegible] [illegible]

15. NIAMD- 6211C-41
SERIAL NUMBER

16. LIST PUBLICATIONS WHICH HAVE RESULTED FROM THIS RESEARCH DURING CALENDAR YEAR 1954:

Ribose Research

Hewitt G. Fletcher, Jr., and Robert K. Ness. Preparation and Properties of 2,3,5-Tri-O-benzoyl-β-D-ribose. J. Am. Chem. Soc., 76, 760 (1954).

Robert K. Ness, Barry W. Diehl and Hewitt G. Fletcher, Jr. New Benzoyl Derivatives of D-Ribofuranose and alpha,beta-D-Ribose. The Preparation of Crystalline 2,3,5-Tri-O-benzoyl-α-D-ribose from D-ribose. J. Am. Chem. Soc., 76, 753 (1954).

Robert K. Ness and Hewitt G. Fletcher, Jr. Preparation and Properties of 1,2-Di-O-benzoyl-1,3-O-(2-hydroxybenzylidene)-D-ribose, an Orthobenzoate Derivative of D-Ribofuranose. J. Am. Chem. Soc., 76, 1663 (1954).

Byproducts

R. Allerton and Hewitt G. Fletcher, Jr. The Acetolysis of Some Carbohydrate Benzyl Ethers. J. Am. Chem. Soc., 76, 1737 (1954).

Hewitt G. Fletcher, Jr., Barry W. Diehl and Robert K. Ness. Methyl 2-Deoxy-furanoside and Certain Other Derivatives of D-Xylose. J. Am. Chem. Soc., 76, 3065 (1954).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS RESEARCH DURING CALENDAR YEAR 1954:

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Carbohydrates
SECTION

4. Bethesda
LOCATION

5. Z1AM-
OMPILL NUMBER

6. Structure of the Carbohydrate Moieties in Steviosides
PROJECT TITLE

7. R. C. Fletcher, Jr.
PRINCIPAL INVESTIGATOR

8. E. E. Ward, Jr. (Fellow)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to elucidate the structure of the carbohydrate moieties in steviosides, the sweet, non-toxic principle of the Paraguayan plant Stevia rebaudiana.

Methods Employed: A variety of chemical degradative methods are employed — methylation, mild glycosyl-cleaving agents, periodate, chromatography, etc.

Major Findings: Two of the glucose residues in steviosides are joined together by a C_2-C_3 linkage and thought to be attached at C_3 to the aglucone. The remaining glucose unit is attached at C_1 to a sterically hindered carbonyl of the aglucone. An hydroxyl group on the latter group is claimed to give lactonization and steviolbioside. This steviolbio is a doubly bad type of stevia labile glycoside.

Significance to NIAMD Research: Basic information regarding the structure of the sweetest naturally occurring substance has been gained.

Proposed Course of Project: The synthesis of glucose derivatives attached at C_3 by sterically hindered acids (i.e. models of steviosides) is being studied by way of obtaining new theory regarding the behavior of steviosides with alkali. This work will be completed within the coming year.

10. BRAND: 6211B-12
SERIAL: [illegible]

11. BURDEN (cfs):

	DESIGNED OPERATIONS	SUBJECT TO ICING			SUB TO ICE			ICING
		RIME	GLAZE	TOTAL	RIME	GLAZE	TOTAL	GLAZE
FY 1955	2,300	½	1	1½	½	1	1½	
FY 1956	2,300	½	1	1½	½	1	1½	

12. FLIGHT ACTIVITY:

[illegible]	☒	[illegible]	☐
[illegible]	☐	[illegible]	☐

13. [illegible] [illegible] [illegible]

[illegible]

19. [illegible] 5211.3-12
[illegible]

16. LIST PUBLICATIONS ISSUED DURING THE [illegible] FOR WHICH COPIES ARE [illegible] 1954:

E. R. Kooi, Jr., E. Allerton, E. V. Stoll and E. G. Fletcher Jr. [illegible] The structure of the mucose [illegible].

E. R. Kooi, Jr. and N. O. Fletcher, Jr. The [illegible] 2,3,4,6-Tetra-O-[illegible] 1-(2,4,6-trimethylbenzoyl)-D-glucopyranose and their Reaction with [illegible]

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING [illegible] YEAR 1954:

None

1. [illegible] Institute of Arthritis and Metabolic Diseases
[illegible]

2. [illegible] 3. [illegible]
[illegible]

4. [illegible] 5. [illegible]
[illegible]

6. [illegible] aromatic amino acids
[illegible]

7. B. Witkop
[illegible]

8. [illegible]
[illegible]

9. PROJECT DESCRIPTION

Project: [illegible] development of synthetic and analytical procedures to permit [illegible] investigations in the conversions of amino acids [illegible] which are [illegible] to be revealed by pathology research methods.

Objectives: We also [illegible] a detailed knowledge of the oxidative [illegible] heterocyclic, aromatic and polycyclic amino [illegible] while the [illegible] of studies of normal intermediates in the [illegible] of physiologically important factors such as amino acids, peptides, vitamins, etc. The availability of such intermediates [illegible] synthesis makes it possible for the biochemist to [illegible] into [illegible] metabolic processes.

Methods Employed: The research [illegible] being developed [illegible] the synthesis of [illegible] such as [illegible] have [illegible] [illegible] [illegible] cultures [illegible] have [illegible] [illegible] the [illegible] the [illegible] of [illegible] has been limited. Special [illegible] techniques [illegible] employed in an attempt to [illegible] [illegible] [illegible] and chemical [illegible] [illegible] [illegible] [illegible] [illegible] methods are being used [illegible] [illegible] [illegible] [illegible] [illegible]

[illegible] Currently, the fundamental problems of [illegible] metabolism have been studied in several ways. The findings have been published in a [illegible] progress report.

Improved [illegible] methods have been developed for the diagnosis of [illegible] heterozygotic and open carriers.

The conversion of histidine (with Dr. Keller) to (allo)hydroxyproline via the new (allo)-hydroxycarbinone was furnished valuable information on stereochemical interrelations and the mechanism of cyclization of open (hydroxy)amino acids into new and known cyclic amino acids.

The transannular interaction of a peptide group has been demonstrated in a model compound for the first time in collaboration with Dr. L. Cohen.

New analytical procedures for the detection of unusual amino acids in microgram quantities have been developed in collaboration with Dr. S. Fisc, NIDR.

Significance to Metabolic Diseases Research: Very recent biochemical and clinical investigations have led to surprising findings concerning the etiology of various [illegible] unknown diseases. Hereditary, nutritional or environmental factors produce deviations from standard metabolic patterns of amino acid degradation. In particular the following diseases have been associated with new or known amino acid metabolites: schizophrenia and other mental disorders, diabetes, and phenylpyruvic oligophrenia.

Further correlations between amino acid metabolites and certain dysfunctions are now at [illegible], but certain mental disorders seem to respond to large doses of glutamic acid or glutamine, possibly also to 5-oxoprolinuric acid (from histidine); certain hemolytic crises lack uracemia in the blood platelets, disturbance in collagen metabolism may point to abnormal oxidation products of hydroxy-proline. In view of all these observations there is a definite necessity for the synthesis of the various missing links which will metabolites whose existence or importance can be [illegible] be tested. A later expansion of this program may have to deal with relating these type of research to the level of peptides and proteins.

Significance to Arthritis: The new analytical procedures for the detection of unusual amino acids when applied to samples of connective tissue of normal and pathological origin will answer a problem of long standing, i.e., are pathological changes in connective tissue accompanied by chemical changes?

Proposed Course of Project: Further effective research following these lines will be attempted on a scale commensurate with the present facilities.

10. NIAMD- 62113-43
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS: PROF	OTHER	TOTAL	MAN YEARS: PROF	OTHER	TOTAL	PATIENT BEDS
FY 1955	14,200	2		2	2		2	
FY 1956	20,200	3	2	5	3	1	4	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL YEAR 1955 OR 1956. IF COOPERATING UNIT IS PUBLIC HEALTH SERVICE, GIVE SERIAL NO(S).

Dr. G. Hämfriand (NMI)
Dr. E. Pias (NIDR)
Dr. A. M. Bowling Green State University
Dr. T. Keller, Stetson University

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH NOW SUPPORTED IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES, OR FUNDS), IDENTIFY SUCH RESEARCH. (BY SERIAL NO(S) IF KNOWN HERE)

None

Persons, Awards, and Publications Data

15. NIAMD- 02110-02
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS THAT HAVE APPEARED DURING CALENDAR YEAR 1954:

B. Witkop. Rearrangements de Cetones, Alcamines, Peroxydes, Oximes et Alcaloides dans la Serie de l'Ecgonine. Bull. Soc. Chim., 425 (1954).

B. Witkop. Infrared Diagnosis of the Hydrochlorides of Organic Bases. I. Spectrophotometric Differences between Anhydrohydrocyclic Bases and their Salts. Experientia, 10, 420 (1954).

B. Witkop. Oxidation Mechanisms. XIV. The Reaction of Trans-Decahydroquinolines with Molecular Oxygen. Experientia, 10, 419 (1954).

A. Ek and B. Witkop. The Cystosis of Labile Hydroxytryptophan Metabolites. J. Am. Chem. Soc., 76, 5579 (1954).

B. Witkop and T. V. Heller. Studies on Schiff Bases in Connection with the Mechanism of Transamination. J. Am. Chem. Soc., 76, 5589 (1954).

B. Witkop. Infrared Diagnosis of the Hydrochlorides of Organic Bases. II. The Structure of Mycosine. J. Am. Chem. Soc., 76, 5597 (1954).

S. Goodwin and B. Witkop. Chemistry of Dihydroxyfumaric Acid. J. Am. Chem. Soc., 76, 5599 (1954).

B. Witkop and J. Patrick. Antihypnotics. II. J. Am. Chem. Soc., 76, 5603 (1954).

B. Witkop, S. Goodwin and T. V. Heller. 5-Hydroxy-5-hydroxymethylhydantoic Acid (Allouan Hydromercuride) and other Allouan Adducts. J. Am. Chem. Soc., 76, 5613 (1954).

J. H. Patrick and B. Witkop. Oxidative Mechanisms. XV. The Conversion of Benzenoxine Hydroperoxides into the Perazine Rearrangement. J. Org. Chem., 19, 1625-1629 (1954).

B. Witkop. Some Novel Aspects of the Chemistry of Emetics. Angew. Chem., 66, No. 23, December 1954.

17. LIST HONORS AND AWARDS TO PERSONNEL VALUABLE TO THIS PROJECT DURING CALENDAR YEAR 1954:

None.

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Analytical
SECTION

4. Bethesda
LOCATION

5. NIAMD - Original
SERIAL NUMBER

6. The Synthesis of Compounds Related Structurally to Reserpine
PROJECT TITLE

7. E.L. Kay and James G. Murphy
PRINCIPAL INVESTIGATORS

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objective: To synthesize psycho-stimulating and/or sedative drugs which have sedative clinical deficiencies side-effects, particularly addiction potential, respiratory depression and nausea.

Methods Employed: Principally, two lines were followed in carrying out this project. In the first a simple Mannich base (I) (1-phenethyl-4(3)-benzylpiperidine) of the potent analgesic dreamed (II) [2-phenethyl-4-(N-propionyl-anilino)-piperidine] was synthesized by an Hofmann process starting from phenylacetonitrile or by a Michael reaction from β-halogenated. This product, studied in 1956, was considered to the early part of 1956.

In the second, a phenolic hydroxyl group was introduced into the benzene portion of 1-(1-[2-thienyl-2-phenylethyl]-4-piperidyl) a compound previously synthesized in an effort to prepare (III) (a potent analgesic activity) to give the analogue (IV) (p-hydroxy, 4-phenyl, 4-ethyl morpher). This synthesis was accomplished in an 11-step scheme starting from p-hydroxyacetophenone. The known procedure for preparing 2-methoxyphenylcyclohexanone, and intermediate had to be modified for adaptation to large-scale runs because large amounts of IV were needed for studies in the monkey. Compounds III and IV might be looked upon as phenolic reserpine types.

Major Findings: Screening of the substances mentioned above as well as some derivatives and intermediates (Methods B, Sidy and Vogt) showed that Compound I and three related substances were somewhat as one-third as effective as reserpine in producing sedation in mice but less toxicity (approximately twice as effective as reserpine. Compound IV and its 3-acetyl derivative were not only ten times as active as III but much less toxic. They are as potent as morphine in mice. Further

area; IV did not exhibit the flexor reaction in mice until the analgesic dose was reached; whereas morphine produces this effect well below the effective dose. Dr. Eddy has judged this compound to be worthy of further (addition) studies in humans.

Course of Projects: During the calendar year 1955, it is planned to modify the structure of the highly active compound IV in such a way as to have a 7-membered N-containing ring in place of the 6-membered or piperidine ring. This same structural variation in the less-active reperidine series, such a modification by other investigators, produces analgesics that appear to have no addiction potential. In addition, the resolution of IV into the optical antipodes is projected; it is anticipated that one isomer is responsible for most or actually all of the activity of IV. Finally, structural alterations of I and derivatives which have a more favorable therapeutic ratio than III, such as the introduction of a p-phenolic group, and/or a 17-methyl substituent, and the increase of the N-containing ring size are now in progress.

10. Name - Symbol
Equity Security

11. Annual Data:

	Authorized Securities	Issued or Outstanding			Held by Issuer			Treasury Stock
		Public	Control	Total	Public	Control	Total	
FY 1959	10,500	1 1/6		1 1/6	1 1/6		1 1/6	
FY 1960	10,500	1 1/6		1 1/6	1 1/6		1 1/6	

12. Issuer Activity:

Dividend ☒ Exchange Privileges ☐

Option & Warrants ☐ Conversion Privileges ☐

13. Identify all convertible debt securities and equity securities issuable upon exercise of options, warrants or conversion privileges. Describe terms of conversion or exercise, terms of any subordination provisions and any restrictions on repurchase or redemption.

None

14. If more than 5% of outstanding equity securities are held by any person, identify such person and state amount owned.

None

10. [illegible]

11. BUDGET DATA:

	Authorized Appropriation	Estimated Obligations			Net Loans			Estimated Loans
		Total	Offset	Gross	Total	Offset	Gross	
FY 1955	$0,500	1 1/6		1 1/6	1 1/6		1 1/6	
FY 1956	$0,300	1 1/6		1 1/6	1 1/6		1 1/6	

12. BUDGET ADDITIVE:

[illegible]	☒	[illegible]	☐
[illegible]	☐	[illegible]	☐

13. [illegible]

None

14. [illegible]

None

15. STAND - 60119-44
SERIAL 70788

16. LIST PUBLICATIONS OTHER THAN THOSE LISTED UNDER PREVIOUS HONORS GRANTED IN 1954:

Structures Related to Morphine. I. 2-(2-Hydroxyethoxyethyl) 3-Morpholinohexanone and Derivatives. O.O. Orazi and E.L. Hirst, J. Org. Chem., 19, 615 (1954).

Structures Related to Morphine. II. An Isomer of 6-Methylmorphinan. E.L. Hirst and J.O. Orazi, J. Org. Chem., 19, 618 (1954).

Synthesis of 6-Dimethylamino-4,4-Diphenylheptane and other Compounds Related to Methadone. O.O. Orazi and S.H. Eby, J. Org. Chem., 19, 773 (1954).

17. LIST HONORS AND AWARDS TO PROFESSIONAL SOCIETIES AND PROFESSIONAL ACTIVITIES IN 1954:

Participated in a panel symposium on "Synthetics and Isomerism" at the 3rd Post Graduate Meeting of the New York State Society of Anesthesiologists in December. The subject of my talk was "Recent Developments in the Field of Analgesics".

Analysis of the morphinan derivatives

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Analgesics
SECTION

4. Bethesda
LOCATION

5. NIAMD- 62119-63
SERIAL NUMBER

6. The synthesis of the isomeric dihydrothebaine degradation products: 1,2,3,4-tetrahydro-1-ethyl-5, 6-dimethoxy-2-methylnaphthalene and 3-propyl-3,4-dihydro-4-ethyl-4-methyl-6,7-dimethoxytetrahydronaphthalene.
PROJECT TITLE

7. Dr. Lewis J. Sargent
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The preparation of the above-named compounds would complete the second half of a model experiment designed to elucidate the chemical structure of the important morphine derivative, [illegible]

Methods Employed: Starting with the newly synthesized key compound [illegible]-(2-chloro-4,5-dimethoxyphenyl)-butyric acid, 1,4-dihydro-1-(2-chloro-4,5-dimethoxyphenyl)-3-hexanol was prepared. Numerous attempts to cyclize the latter to the desired naphthalene derivative failed and led, instead, to the corresponding unsaturated hexene derivative. Despite the use of rather rigorous conditions, the latter substance also resisted cyclization (for steric reasons?) and was recovered largely unaltered.

In another approach, the above key butyric acid was cyclized to the expected tetrahydronaphthalenone which, after treatment with ethyl magnesium bromide and catalytic dehalogenation afforded 3-hydroxy-4-ethyl-4-hydroxy-5,6-dimethoxy tetrahydronaphthalene. This substance differs from one of the desired degradation products only in having a hydroxyl in place of an alkyl group on the geminal carbon-4. The replacement of the hydroxyl by ethyl will be studied.

A third, and what appears to be the most promising, approach originated with 7,8-dimethoxytetralone-2. It has been possible, by utilizing a two step process, to dialkylate carbon-1 to yield

9. Project Description - Continued

3-ethyl-3-methyl-1,5-dimethoxypiperidine-2. Apart from steric considerations, the latter should be accessible to the corresponding tertiary carbinol (via propyl magnesium bromide or propyl lithium) which upon dehydration and hydrogenation of the resulting olefin should lead to one of the two isomeric cyprenorphine products.

A fourth primary utilizing the free-radical induced addition of maleic anhydride to 3-(3,3-dimethylpropyl) pethidine has been examined cursorily. Results thus far indicate that upon working out proper reaction conditions, this method may prove to be of value in

Significance to Analgesic Research: Clinical studies have demonstrated that [illegible] may be a more powerful analgesic than morphine with less addiction liability. Since one of the most important goals of analgesic research is complete absence of the physical dependence liability from analgesic potency, other knowledge regarding the structure of [illegible] may serve to suggest other avenues of research insofar as (a) modifying the [illegible] or (b) ameliorating related substances are concerned.

Proposed Course of Project: The four approaches outlined above will be thoroughly investigated and, should the need arise, other methods will be devised and studied.

[illegible] portion of [illegible] research and published results.

10. HEADQ. 5213-45
SERVICE WORKER

11. BUDGET DATA:

	EXISTING MANPOWER	CURRENT REQUIRED			1ST YEAR			PROJECT DATE
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1965	10,100	1		1	1		1	
FY 1966	10,100	1		1	1		1	

12. BUDGET ACTIVITY:

PROPOSED [X] ACCEPTED [ ]

STATUS OF APPROVAL [ ] TENTATIVE ASSURANCES [ ]

13. INDICATE ANY KNOWLEDGE HELD OF THE PUBLIC HEALTH PROGRAMS OF OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR CONSULTANT AID FOR THIS PROJECT IN FY 1965 OR 1966. IN COOPERATION MUST BE STATED EVEN IF NONE IS KNOWN.

None

14. IF THIS PROJECT REQUIRES, STIMULATES, OR FACILITATES PERSONS BEING TRAINED IN THE PUBLIC HEALTH SERVICE (WITHOUT REGARD TO SOURCE OF FUNDING), EXCLUDING FUNDS, IDENTIFY SUCH PERSONS. (SEE ITEM 14(5) IF "NONE" IS)

None.

15. NAME: [illegible]
SMALL PHASE:

16. LIST PUBLICATIONS DURING THIS PERIOD OR PROJECTED FOR THE FOLLOWING PERIOD:
1954:

Sargent, Lewis J. The Synthesis of 1-Ethyl-, 2-Ethyl-, 3-Ethyl- and 4-Ethylacridine. J. Org. Chem., 19, 599 (1954)

Sargent, Lewis J., and Small, Lyndon F. Carbinolamines Derived from 7-Chloro-2-methyl-1,2,3,4-tetrahydroacridines as Plasmodicides. J. Org. Chem., 19, 1000 (1954)

17. LIST MEETINGS AND TRAVEL TO BE ATTENDED OR UNDERTAKEN IN THE FOLLOWING CALENDAR YEAR 1954:

None.

1. National Institute of Arthritis & Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Analgesics
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62119-03
SERIAL NUMBER

6. The Synthesis of 6-Amino-4,4-Diphenyl-3-Heptanone, the Primary Amine Corresponding to Methadone
PROJECT TITLE

7. E.L. May
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objective: To synthesize the title compound above for evaluation as designed to shed light on tolerance, physical dependence, etc. of narcotics.

Methods: Although several approaches for synthesizing this new compound have been tried, none has yet proved successful. The major obstacle appears to be the great facility with which necessary intermediates cyclize to pyrrolidine derivatives. A new sequence of reactions is now being investigated which involves protection of reactive centers in the intermediate molecules. For example, the starting ketal, [illegible] 2,2-Diphenyl-5-butanone ethylene ketal, is being prepared as an intermediate. This work will continue.

10. MIAD - 62139-46
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF.	OTHER	TOTAL	MAN YEARS PROF.	OTHER	TOTAL	PRESENT DATE
FY 1955	2,600	1/3		1/3	1/3		1/3	
FY 1956	2,600	1/3		1/3	1/3		1/3	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OR THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THE PROJECT IN 1955 OR 1956. IF COOPERATING UNIT IS USPHS, GIVE ESTIMATE DOLLAR AMOUNT (S)

None

14. IF THIS PROJECT DUPLICATES, COMPLEMENTS, OR PARALLELS RESEARCH OR TRAINING IN THE PUBLIC HEALTH SERVICE (WITHOUT CONSIDERATION OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF KNOWN)

None

15. NIAMD - 62119-46
SERIAL NUMBER

16. LIST PUBLICATIONS UNDER THIS SERIAL NUMBER DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL WORKING UNDER THIS SERIAL NUMBER DURING CALENDAR YEAR 1954:

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Analytical
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62110-67
SMITH, HUMAN

6. Chemical Structure and Analgesic Action
PROJECT TITLE

7. Nathan B. Eddy
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To ascertain chemical structure requirements for analgesic activity, and as far as possible, differentiate them from the chemical features related to toxic effects and undesirable liability of the same compounds. This is a part of the over-all attempt to obtain better pain relief with less accompanying toxic reactions and addiction liability.

Methods Employed: By the hot plate method originated in this laboratory, compounds of many chemical types and widely varying potency, usually related one to another, are screened for analgesic activity. As a corollary of the investigation, toxicity of active compounds is determined. We are also attempting to correlate the probable reasons for possible and visible differences in effectiveness of similar compounds when given orally or subcutaneously. The techniques employed are fully described. For example of potential liability, see Item 13. This is, of course, a continuous project which can only point on for years and only tentative conclusions can be drawn at any particular time. There are currently being commenced on a comprehensive endeavor (see Item 17.) but a very important development in the investigation of compounds made or not made is the demonstration in a number of the group of analgesic action equivalent to that of morphine. That group of compounds may be best known as considered as intermediary in the synthesis of morphine. However, this finding assumes very important in the overall objective. Additional quantities of the compound are being prepared for additional liability studies.

10. [illegible]
[illegible]

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions			Salaries			Travel Costs
		Exempt	Career	Total	Exempt	Career	Total	
FY 1955	$7,300	1 1/6	2	4 1/6	1 1/6	3	4 1/6	
FY 1956	$7,900	1 1/6	2	4 1/6	1 1/6	3	4 1/6	

12. BUDGET ACTIVITY:

[illegible] ☒ [illegible] ☐

[illegible] ☐ [illegible] ☐

13. [illegible] THE [illegible] THE [illegible], [illegible] [illegible] [illegible]

15. [illegible]

16. List publications since 1954 not already listed [illegible]

1954:

Leimgruber, Dorothy and Eddy, Nathan B.

Synthetic analgetics XII. [illegible]

J. Pharmacol. & Exper. Therap., 110: 135-141, 1954.

17. List medical societies to which elected [illegible]

since 1954:

Temporary consultant to the World Health Organization to prepare report referred to in collaboration with a representative from the General Assembly of the United Nations.

Chairmanship of panel discussion, Pathological Aspects of the [illegible] Society of Anesthesiologists, held San Juan, P.R., December 11, 1954. (Due to illness, Dr. Eddy [illegible] Assembly for [illegible]

Attachment 2 | Protocol for IND Package Submission

Veterans Investigation Board

1. Name and Address of Investigator and Associate Investigators
[illegible]

2. Phase of Investigation
[illegible]

3. Investigation Entitled
[illegible]

4. Synonyms

5. Study - Single Blind, Double

6. Study of oral pain relief in human with [illegible]

7. Author [illegible]

8. Joseph Cowin
[illegible]

Project Description

Objectives: a) To determine efficacy of the [illegible] in relieving [illegible] b) To [illegible] side effects in patients with [illegible] type of pain, as a part of the overall effort to discover [illegible] relief of pain.

b) [illegible] for which may be present are [illegible] agents. Evidence is available that it may be possible to avoid [illegible] w/multiplicity and [illegible] tolerance and addiction liability by the simultaneous use of [illegible]. The purpose is [illegible] and efficacy of such a procedure. It would be [illegible] to the overall effort of [illegible] pain relief.

Methods Employed: a) [illegible] [illegible] duration of a standard analgesic, a placebo, and the one [illegible] agent, drugs will be administered to patients with [illegible] pain in a series of [illegible] where the pain is persistent enough to permit the administration of [illegible] five. Only two sets of the [illegible] per day, randomized between [illegible] relief. b) Observations of severity of pain and degree of pain relief and incidence of undesirable side effects will be made at [illegible].

Analysis of Air Weather Activities (Surface)

An examination of the effect of integrators on relevance and response development, again using as far as possible, the double-blind technique, paired subjects without previous material narrative experience, but with persistent pain, will be [illegible] a standard analysis along the same lines as the new subjects with the exception only of a selected number of case-pairs. There will be periodic determination of the degree of tolerance and dependence present in each of the patients. Terminal cancer patients suitable for this purpose will be the best available clinical [illegible]

10. NAME - 52119-MD
SERIAL NUMBER

11. BUDGET DATA:

	DESIGNATED MAINTENANCE	BUDGETED POSITIONS			SEP YEARS			REMARKS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	15,300	1 1/2	1/3	1 5/6	1 1/3	1/3	1 5/6	
FY 1956	15,300	1 1/2	1/3	1 5/6	1 1/3	1/3	1 5/6	

12. BUDGET ACTIVITY:

RESEARCH ☑ ADMINISTRATION ☐

DEVELOPMENT & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY THE MODIFICATIONS MADE IN THE PUBLIC HEALTH SERVICES, OR OTHER GOVERNMENTAL SERVICES, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL YEAR 1955 or 1956. (IF NONE, SO STATE.)

None

14. IF THIS PROJECT RESULTED, DIRECTLY OR INDIRECTLY, IN PARALLEL DEVELOPMENT IN THE PUBLIC HEALTH SERVICE (WITHOUT DUPLICATION OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH DEVELOPMENT. (SEE SECTION 314 (B) OF ACT.)

None

15. NIAID - 5012-40
Sanofi Winthrop

16. LIST PUBLICATIONS OTHER THAN PROGRESS REPORTS ON THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PROFESSIONAL STAFF ON THIS PROJECT DURING CALENDAR YEAR 1954:

None

[illegible] Investigator Grant

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Analytical
SECTION

4. Bethesda
LOCATION

5. [illegible]
[illegible]

6. The study of the three-dimensional aspect of certain organic molecules
PROJECT TITLE

7. Stephen F. Findlay
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The preparation of appropriate derivatives of optically active plant alkaloids, the search for better methods of determining important plant alkaloids, the isolation of minor alkaloids are being investigated and the number of such other investigations as prove results of particular significance to fundamental or to applied chemistry.

The object immediately in view is the preparation and differentiation of the two possible stereoisomers of the pseudo-cocaine.

Methods Employed: The methods employed in the investigation of the past year were those typical of research in organic chemistry.

Major Findings: The major finding of this project during the past year was the deduction of the three-dimensional structure of the pseudo-cocaine.

Significance to NIAMD Research: The fore-going finding permitted the correction of a solution to this structural problem proposed about a year earlier by a foreign investigator; permitted the correction of structures assigned to related compounds; demonstrated the applicability of certain recently developed stereochemical principles to problems of considerable importance in organic chemistry; and provided a convenient means of converting cocaine into benzoyl-ecgonine or of pseudococaine.

15. NIAMD - 03119-A9
SERIAL NUMBER

16. LIST PUBLICATIONS UNDER THIS PROJECT DURING CALENDAR YEAR 1954.

The three-dimensional Structure of the cocaines. Part I. Cocaine and Truxillococaine," Journal of the American Chemical Society, To: 2955-2964. 1954

17. LIST HONORS AND AWARDS TO PERSONNEL RELATED TO THIS PROJECT DURING CALENDAR YEAR 1954.

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Analytical
SECTION

4. Bethesda
LOCATION

5. Fiscal Year 1962
FISCAL YEAR

6. Studies in the Synthesis of Chemical Compounds of Possible Chemotherapeutic Interest.
PROJECT TITLE

7. T.D. Perrine
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: The object is to develop methods of chemistry for certain chemical systems, to develop methods for the purification and isolation of such compounds, and to prepare certain substances for physiological testing.

Methods Employed: Studies are under way to develop the synthesis of hydroxyquinolidine and of thiocarbolines. Each of these compounds are desired for physiological testing. Use also attempting to find correlation of structure with absorption spectra of analogous compounds.

Proposed Course of Project: These studies will be continued until satisfactory results are obtained.

10. NIAID - 62119-50
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BORROWED POSITIONS PERM	OTHER	TOTAL	A.D. YEARS PERM	OTHER	TOTAL	PROJECT DATE
FY 1955	9,400	1		1	1		1	
FY 1956	9,400	1		1	1		1	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL SERVICES [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OTHER AGENCIES, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN 1955 or 1956. IF COOPERATING UNIT IS OUTSIDE THE FEDERAL GOVERNMENT (E)

None

14. IF THIS PROJECT ASSOCIATES, CONTRIBUTES, OR INVOLVES RESPONSIBILITY IN THE PUBLIC HEALTH SERVICE (WITHOUT EXPENDITURE OF FUNDS), OR FUNDS), JUSTIFY SUCH ASSOCIATION. (SEE SECTION 10, (E) IN GUIDE)

None

15. NIH-M - 6010-50
SOCIAL SECURITY

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS THAT HAVE RESULTED FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Rapoport, H.D. and May, L.L. "Synthesis of 5-Diazo-4-androsten-3,17-dione" J. Org. Chem. 19: 773. (1954)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATED TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

N.I.H. -
December 1960

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Analgesics
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62119-C1
SERIAL NUMBER

6. Analgesics based on Aminoethanonaphthalenones and Aminooctahydrophenanthrenes
PROJECT TITLE

7. James G. Murphy
PRINCIPAL INVESTIGATOR

8. Everette L. May
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objective: Aminoethanonaphthalenones - The objective of this work has been the preparation of substances of type I (2,5-Dimethyl-11-methoxy- or methoxy-9-oxo-6,7-benzomorphan) a five step synthesis (reasonable yields at every step) led to substance II (2,5-dimethyl-9-oxo-11-methoxy-6,7-benzomorphan methobromide) the next step, proligation of II to I (about 10 Mg), proved to be not a simple operation. More than one product is formed. One of these appears to be III (3,4-dihydro-4-(2-dimethylaminoethyl)-4-methyl-2(1H) naphthalenone. Although I has not yet been isolated, it is sustained that this problem will yield to further effort.

Aminooctahydrophenanthrenes - The objective of this work has been the preparation of amines based on the ring system of dibenzocyclohexanethrene, VI, for evaluation as analgesic agents.

This substance appeared worthy of consideration because it is a replica of the hydrogenated phenanthrene ring system of morphine the aromatic ring except in proper position and rings B and C both cis-locked as in the natural alkaloid. The ketone, V (9-oxo-cis-cis-octahydrophenanthrene) 2-phenylcyclohexanone in a three step synthesis. A Mannich reaction on this gave the aminophenanthrene VI. (10-Dimethylaminomethyl-9-oxo-cis-cis-octahydrophenanthrene).

The derived alcohol and acetylated compound, VII (10-Dimethylamino-methyl-9-hydroxy-cis-cis-octahydro-phenanthrene) and VIII. (9-Acetoxy-10-dimethyl-aminoethyl-cis-cis-octahydrophenanthrene)

VI, VII, and VIII have been submitted for evaluation as analgesic agents, of which the first two are now known to be active substances.

The activity found in this series is all the more interesting

In this:

1. The economic do not have a particular purpose.
2. The decision is separated by one person from the possible it would have to pursue to be a more remote future ends.

10. NIH [illegible]

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	ADDITIONAL POSITIONS PROF.	OTHER	TOTAL	NO. OF PERS. PROF.	OTHER	TOTAL	PROJECTED GRANT SUPPORT
FY 1955	0,000	1		1	1		1	
FY 1956	0,000	1		1	2		2	

12. BIOLOGICAL ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

TESTING & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. DESCRIBE ANY CONSIDERATIONS UNIQUE TO THE PUBLIC HEALTH SERVICE, INCLUDING SPECIAL AUTHORITIES, APPROPRIATED FUNDS, FACILITIES, OR PERSONNEL FOR ACTIVITIES [illegible] 1955 or 1956. IF CONSIDERING WHICH IS ACTUALLY OR ULTIMATELY ESSENTIAL TO [illegible]

14. IF THIS PROJECT NECESSITATES ADDITIONAL OR DIFFERENT FACILITIES OR EQUIPMENT IN THE PUBLIC HEALTH SERVICE (WITHOUT EXPENDITURE OF APPROPRIATED FACILITIES OR FUNDS), IDENTIFY SUCH REQUIRED. FOR GENERAL NIH [illegible] ACTIVITY:

None

15. [illegible] - 6211s-21
Serial Number

16. List publications cited in [illegible] 1954:

Structures Related to Morphine. I. 2-(2-Dimethylaminoethyl)-3-benzylhexamine and Derivatives, J.D. Rutgy and E.L. May, J. Org. Chem., 19, 615-27 (1954).

Structures Related to Morphine. II. An Isomer of 3-Methylmorphinan, E.L. May and J.D. Rutgy, J. Org. Chem., 19, 913-29 (1954).

Structures Related to Morphine. III. E.L. May and J.D. Rutgy (In press).

17. List patents [illegible] 1954:

None.

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Steroid
SECTION

4. Bethesda
LOCATION

5. Z1AM - 00120-08
Serial Number

6. The Spectral Characterization of Benzenoid Systems Derivatives [illegible]
PROJECT TITLE

7. Irving Secoy and William R. Nes
PRINCIPAL INVESTIGATORS

8. Ph. D. Scholar
OTHER INVESTIGATOR

9. PROJECT DESCRIPTION:

Methods Employed: The nonsteroids and the anthranilamide amino (reagent) respectively, a tetrahydrobiphenyl benzamide ring [illegible] cyclic simulation and a pentamethylated benzenoid ring with linear simulation have been characterized by their absorption in the spectral regions from 240-400 mμ, 1650-2545 cm^{-1}, and 700-730 cm^{-1}. [illegible] entation of the two classes of compounds is possible in either the infrared or ultraviolet region. The spectra of some related aromatic compounds are discussed in this connection.

Significance to NIAMD Research: This study is an extension of the utility [illegible] this section of characterization and identification (quantitative determination) of steroids which [illegible] being about time and labor saving short cuts in analytical procedures.

10. [illegible]

11. [illegible]

	Estimated Expenditures	Authorized Positions			U.S. Taxes			Contract Costs
		Mgt	Other	Total	Mgt	Other	Total	
FY 1955	9,400	5/6	1	1 1/3	5/6	0	1 1/3	
FY 1956	9,400	5/6	1	1 1/3	5/6	0	1 1/3	

12. [illegible]

Research ☐ Administration ☐

Depts & Divisions ☐ Technical Assistance ☐

13. [illegible]

None

14. [illegible]

None

16. LIST PUBLICATIONS ISSUED DURING THE CONTRACT PERIOD OF THIS PROJECT (1 JULY 1954 - 30 JUNE 1955):

"Detection of Steroidal Pseudosapogenins by Infrared Spectroscopy", by A.L. Morgan, Ph. D. Scallen and I. Schwerr, Anal. Chem. 28, 550 (1956).

"The Spectral Characterization of Sensenoid Systems Particularly from 20(?) Steroids", by Irving Schwerr, William A. Hoe and Phyllis H. Scallen, J. Am. Chem. Soc., 77, 4080 (1955).

17. LIST NAMES OF LEADS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Physical
BRANCH

4. Bethesda
LOCATION

5. [illegible]
SMALL GRANT

6. Complete Structural Elucidation of Veratrine and Solanaceous
PROJECT TITLE

7. Yoshio Sato
PRINCIPAL INVESTIGATOR

8. H.O. LaMer, Jr.
OTHER INVESTIGATOR

9. PROJECT DESCRIPTION

Methods Employed: Veratrine was found to be a mixture of [illegible] alkaloids. The latter have been transformed to crystalline solid derivatives and subsequent reduction to veratridine, a new alkaloid (previous to at C-17) [illegible]. A third alkaloid [illegible] has been isolated in an analogous manner from veratrine. Further, veratramine has been found and [illegible] of this type of alkaloids.

Studies are under way to establish the structure of the alkaloid from sarcopetalum [illegible], with treatment of the [illegible] of veratridine and veratramine.

A natural oxy-genanol alkaloid in the [illegible] of veratrine (from the Indian species Veratrum [illegible]) has been isolated and studied.

Significance to NIAMD research: 1) Theoretical. The alkaloids [illegible] an important group of steroidal alkaloids. These compounds are closely related to the [illegible] due to the research on "Steroidal Saponins".
2) Practical. The plants producing veratridine are [illegible] to be possibly developed as an industrial crop and thus, become [illegible] sources for the production of steroidal hormones, [illegible]

10. [illegible]

11. [illegible]

	[illegible]	[illegible]			[illegible]			[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
FY 1955	16,300	1	1	4	1	1	2	
FY 1956	16,300	1	1	2	1	1	4	

12. [illegible]

[illegible] [illegible] [illegible] [illegible]

[illegible] [illegible] [illegible] [illegible]

13. [illegible]

None

14. [illegible]

None

15. [illegible]
[illegible]

16. [illegible]
1956.

None

17. [illegible]
YEAR 1956.

None

10. [illegible]

11. [illegible]

	[illegible]	[illegible]			[illegible]			
		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
FY 1955	13,000	4½	½	5	4½	½	5	
FY 1956	14,000	4½	½	5	4½	½	5	

12. [illegible]

[illegible] ☒ [illegible] ☐

[illegible] ☐ [illegible] ☐

13. [illegible]

[illegible]

14. [illegible]

[illegible]

15. [illegible]
[illegible]

16. [illegible]
1954.

"Identification of Certain Di-amides and Hydrazones in Steroid[illegible] Paper Chromatography" by L.F. Fieser, [illegible], J. Am. Chem. Society, 76, 1954 (1954).

"Determination of Ethynodiol Diacetate in Tablets" by D. Williams and D.F. Johnson, Anal. Chem. 25, 929 (1953).

17. [illegible]
1948 1954.

None

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Steroids
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62120-55
SERIAL NUMBER

6. The Synthesis of Corticoid Glucuronides
PROJECT TITLE

7. Edward H. Fry
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The synthesis of the glucuronides (i.e., the β-D-glucopyranuronic acids of corticoids (desoxycorticosterone, cortisone, hydrocortisone and others).

There is sufficient evidence that corticoids are present in urine at least in form of glucuronic (particularly an appreciable amount of hydrolysate with β-glucuronidase). A synthesis would establish this point beyond doubt and would, moreover, provide materials to study the various hydrolytic procedures employed more or less empirically at present in the analysis of corticoids.

The synthesis of glucurono-4,6-lactone has unfortunately the purpose of seeing whether or not this compound is a suitable intermediate for the preparation of the ethyl β-D-glucopyranuronic needed in model studies.

Significance to NIAMD Research: Direct connection with the project on "Studies of Individual corticoids", defrayed

10. FUND - 52120-55
SERIAL NO. 358

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	ADDED POSITIONS PROF	ADDED POSITIONS OTHER	ADDED POSITIONS TOTAL	MAN YEARS PROF	MAN YEARS OTHER	MAN YEARS TOTAL	PILOT DATE
FY 1955	11,700	1	½	1½	1	½	1½	
FY 1956	11,700	1	½	1½	1	½	1½	

12. BUDGET ACTIVITY:

RESEARCH ☑ ADMINISTRATION ☐

TRAINING & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN CURRENT 1955 or 1956: IF COOPERATION NOT TO BE DETERMINED AT PRESENT, SO STATE.

None

14. IF THIS PROJECT DUPLICATES, COMPLEMENTS, OR PARALLELS ANOTHER PROJECT IN THE PUBLIC HEALTH SERVICE (PROJECT 1, EXCHANGE OF PERSONNEL, FELLOWSHIPS, FUNDS), IDENTIFY SUCH PROJECT: (OC SERIAL NO. (S) IF KNOWN)

None

15. NIAID - 60120-55
SERIAL NUMBER

6

16. LIST PUBLICATIONS ONLY--NIH GRANTEES FOR THEIR FISCAL YEAR ENDING JUNE 30, 1954:

None

17. LIST ACTIVE NIH AWARDS IN PROGRESS AS OF THE END OF THE FISCAL YEAR 1954:

None

1. National Institute of Scientific and Technical Research
Argentina

2. Academy
Australia

3. Research
Canada

4. Research
Czechoslovakia

5. Research Institute
Hungary

6. The Study of Plant Diseases
Pakistan

7. Indian Lac Research
Research Institute

8. Pest Control Laboratory
Union of South Africa

9. Project Completed

Insects Ecology: A new series of studies have been undertaken to investigate the ecology of insects in relation to their environment. Data collected on the biology and ecology of the following species are being analysed: [illegible] Work on these projects is continued.

Physiology of Insect Diapause: Work on various aspects of diapause in insects is continued. Studies on the effects of [illegible] on the diapause of [illegible] have been completed and a manuscript prepared. Other studies [illegible] are in progress.

10. NIAMD - 6W182-56
SCALE NUMBER

11. BUDGET DATA:

	ACTIVITY SERVICE UNITS	PROFESSIONAL POSITIONS			NON-PROFESSIONAL			FACILITY AREA
		FTE	OTHER	TOTAL	FTE	OTHER	TOTAL	
FY 1955	22,100	2	1½	3½	3	1½	3½	
FY 1956	22,700	2	1½	3½	3	1½	3½	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

PATIENT CARE [ ] TRAINING [ ]

13. IDENTIFY ALL COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OTHER ORGANIZATIONS, INSTITUTIONS, FACILITIES, OR RESOURCES FOR WORK PROPOSED IN FISCAL YEAR 1955 OR 1956. IF COOPERATION HAS BEEN ESTABLISHED, INDICATE BRIEFLY THE NATURE OF THE COOPERATION:

Section on Fermentation, and Institute Laboratory of Biochemistry and Nutrition: NIAMD 6W182-NIAMD- 6216-26

14. IF THIS PROJECT INVOLVES THE USE OF RADIOISOTOPES, OR OTHER RADIATION HAZARDS, IN THE SPACE DESIGNATED FOR THIS PROJECT, INDICATE THE NUMBER OF CURIES, MILLICURIES, OR MICROCURIES OF EACH RADIOISOTOPE, AND THE MAXIMUM ENERGY LEVEL OF EACH RADIATION. (SEE SECTION VII, (E) OF INSTRUCTIONS)

None

15. NIMH - 62140-55
SERIAL NUMBER

16. LIST PUBLICATIONS ORIGINATING FROM, OR RESULTING FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONS RECEIVING A PART OF THEIR SALARY DURING CALENDAR YEAR 1954:

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Steroids
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62.20-ST
Small Grant

6. The Structure of the Aglycone of Steviosides
PROJECT TITLE

7. Erich Mosettig and William H. Lee
PRINCIPAL INVESTIGATORS

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Methods Employed: "Steviol" and "isosteviol" ($C_{20}H_{30}O_3$) [illegible] and mild conditions respectively of [illegible], the primary constituent of Stevia rebaudiana Bertoni (Bridel and Lavielle), [illegible] were shown to be an unsaturated hydroxy acid (monobasic, crystallizing/[illegible] stevic acid), and a saturated keto acid respectively, (renamed keto isosteviol acid), by characterizing the functional groups chemically and spectroscopically. Particularly by the [illegible] hydrogenation of isosteviol to dihydrogen and by the spectroscopic comparison (C.F. and I.R.) of steviol and phyllocladene and [illegible] for the aglycones of [illegible] of diterpenoid acids containing the skeleton of a perhydrophenanthrene with a cyclopentane ring fused to C-8 and to C-11.

Significance to NIAMD Research: The significance is [illegible] so far no glycosides of a diterpenoid acid [illegible] been found in nature. An outstanding novelty is the [illegible] rearranging power of the trichloride of this diterpenoid acid and the nearly complete physiological [illegible] of the latter.

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Steroids
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62CB-5I
STAFF TYPE

6. The Structure of the Aglycone of Steviosides
PROJECT TITLE

7. Erich Mosettig and William R. Hoe
PRINCIPAL INVESTIGATORS

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Methods Employed: "Steviol" and "Isosteviol" ($C_{20}H_{30}O_3$) obtained on degradation and acid hydrolysis respectively of steviside, the principal constituent of Stevia rebaudiana Bertoni (Bridel and Lavieille), were shown to be an unsaturated hydroxy acid (non enolic, contained dehydrohydroxy cyclic acid), and a saturated keto acid respectively, (renamed keto kaurenic acid), by characterizing the functional groups chemically and spectroscopically. Particularly by the dehydrogenation of isosteviol to phenanthrene and by the spectroscopic comparison (U.V. and I.R.) of steviol and phyllocladene was confirmed for the aglycones of furanoid of diterpenoid acids containing the skeleton of a perhydrophenanthrene with a cyclopentane ring fused to C-2 and to C-11.

Significance to NIAMD Research: The significance is presently theoretical inasmuch as far no glycoside of a diterpenoid acid has been found in nature. Its outstanding novelty is the structural resemblance of the triglucoside of this diterpenoid acid and the nearly complete physiological inertness of the latter.

Budget Data Sheet

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	ESTIMATED POSITIONS			MAN YEARS			FUTURE YEARS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$9,400	2/3	1/3	1 1/6	2/3	1/3	1 1/6	
FY 1956	$9,400	2/3	1/3	1 1/6	2/3	1/3	1 1/6	

12. BUDGET ACTIVITY:

ADMINISTRATIVE ☒ ADMINISTRATIVE ☐

DIVISION A APPROVAL ☐ TECHNICAL AS IS FILED ☐

13. IDENTIFY ANY OF OPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL YEAR 1955 or 1956. IF COOPERATING UNIT IS NIH, USE EXTRA SPACE IN ITEM 14.

None

14. IF THIS PROJECT RESULTED, OR IS EXPECTED TO RESULT, IN THE PUBLIC HEALTH SERVICE OBTAINING TEMPORARY OR PART-TIME SERVICES OF PERSONS, IDENTIFY SUCH AND STATE [illegible] (USE EXTRA SPACE IN ITEM 13 IF NEEDED)

None

15. Item - 60.33-51
Serial Number

16. List publications (and their locations) not more than 5 years old. None

17. List patents and patent applications in this subject. Under 5 years
Year 1954:

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Chemistry
LABORATORY

3. Steroids
SECTION

4. Bethesda
LOCATION

5. NIAMD- 62120-59
ANIMAL NUMBER

6. Elucidation of the Stereochemistry of the Spirocentral Side Chains of Steroidal Sapogenins.
PROJECT TITLE

7. Irving Scheer and Rajko Kostetig
PRINCIPAL INVESTIGATORS

8. R.D. Kostic
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: Recent studies (Scheer, Kostic, Kostetig) have established the isomerism at C-25 in steroidal sapogenins. A possibility of assigning rigidly the existence of non-equivalence of a (pseudoaxial) epimeric methyl at C-22 offered itself through the recently discovered (Prof. Barton in Manchester, England), and biogenetically evident occurrence of (+)-diosgenin, the cholestanine. In a cooperative project with Prof. Barton and the Eastern Research Laboratory of the Department of Agriculture we are first attempting to confirm the proposed structure of the cholestanine, and then transform them into the desired C-22 epimeric sapogenins (eliminating asymmetry at C-25).

In extension of the studies of the C-25 isomerism the hitherto unknown and inaccessible 16-hydroxyneoperuvoses and 16-hydroxyneoruscogenins were obtained in a descriptive process starting from the 3-acetate of 5α-dehydrotrahydro-gamma-sarsasapogenin (or -smilagenin) and the corresponding tigogenin derivative respectively. The many more epimeric 16-ketones were obtained in excellent yields by a similar procedure from the 3,16-diacetate or trimesylate of tetrahydro-gamma-sarsasapogenin (or -smilagenin).

Significance to NIAMD Research: a. Theoretical. The above studies were prompted by substances which have been hitherto unavailable and are of great importance in respect to spectroscopic studies and possibly as metabolic intermediates (16-hydroxy). Furthermore, in these studies the entirely unorthodox situation has been discovered, that compounds that have identical melting points give no admixture melting point depressions, have practically identical rotations, and have identical infrared spectra, may be different.

b. Practical. Steroidal sapogenins are potential precursors of the synthesis of steroidal hormones, including cortisone. The [illegible] farm of plants containing the sapogenins, as an [illegible] crop is being undertaken by the Department of Agriculture.

10. ATLAS - (21-20-52
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	MAN YEARS						PROJECT DATE
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	14,300	1 1/3	1/3	1 5/6	1 1/3	1/3	1 5/6	
FY 1956	20,900	1 1/3	1/3	1 5/6	1 1/3	1/3	1 5/6	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL 1955 or 1956. IF COOPERATING UNIT IS WITHIN PHS INDICATE SERIAL NO. (S)

Eastern Utilization Research Branch of the U.S. Department of Agriculture, Philadelphia, Pennsylvania.

14. IF THIS PROJECT DUPLICATES, SUPPLEMENTS, OR PARALLELS RESEARCH BEING CONDUCTED IN THE PUBLIC HEALTH SERVICE (ACTIVITY INVOLVED OR NATURE OF RESEARCH, FACILITIES OR FUNDS,) IDENTIFY SUCH RESEARCH : (BY SERIAL NO. (S) IF WITHIN PHS)

None

15. NIH(A) - 60120-59
SMITH, KLINE

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1958:

"The 6-25-Isomerism of Sarsasapogenin and Smilagenin", by I. Scheer, R.B. Kostic and E. Rosetta, in press, J.A.C.S. 77, pp.... (Feb. 1955)

"Coprostane, Cholestane, and their 16- -Hydroxy Derivatives from Sarsaparilla Sapogenins", by I.Scheer and E. Rosetta, in press, J.A.C.S. 77, pp.... (1955)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1960

Analysis of the Digestive Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pathology and Histochemistry
LABORATORY

3. Histochemistry
SECTION

4. Bethesda
LOCATION

5. NIAMD-61121-60
GRANT NUMBER

6. Development and exploration of histochemical reactions in tissues
PROJECT TITLE

7. R. D. Lillie
PRINCIPAL INVESTIGATOR

8. J. B. Longley, R. C. Rahn
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To further correlate chemical and morphologic structure of normal and diseased tissues by decking or unmasking chemical reactions by histologic change and to explore and interpret existing chemical and empirical methods.

Histochemical studies of normal and pathological pigments already indicate that nerve cell melanin is chemically distinct and probably functionally different from meningeal, ocular, cutaneous and tumor melanins. Chemical distinctions are also appearing among the lipofuscin pigments, intimating diversity of chemical origin and significance and perhaps metabolic function of these bodies.

The presence of distinct anthracharmalin substances in different mammalian species appears to be demonstrated and is now under investigation.

These studies entailed the exploration and introduction into histologic technic of alkylene cyanin as a more suitable resinous mounting medium for unstained sections.

Studies of histochemical enzyme localizations in the renal tubule indicate a diversity of function as well as morphology in the several segments of the nephron. This study has involved devising of new and more rapid reconstruction technics to permit precise localization in the various parts of the renal tubule.

The histochemical significance of the hitherto purely empirical hematoxylin methods is under study and it appears that neither phosphoric acid moieties nor desoxyribose aldehyde are responsible

9. Project Statement - Continued

for the reaction. A series of other polynucleotides can be synthesized in some of the reactions. This gives a polynucleotide reaction by intercalating and triangulation, distinct from the depolymerization reaction, which may account for some of the confusion in the literature.

Localization methods for ribosome and the isolated nucleotides are under study with some preliminary data indicating the possibility of a successful, fairly specific localization of ribosome.

Joint studies with E. Lederer's group on antibiotic changes in ACTH producing tumors are affording opportunity for biochemical as well as chemical characterization of this hormone. Microchemical studies with E. T. Bates have led to the characterization of "glycosamin".

Significance to Health Research: As new methodology is derived, and its [illegible] of these methods are made available, any general understanding of the evolution of disease processes from a molecular correlated morphologic and chemical standpoint, will become [illegible].

The improvement in understanding of disease processes increases their susceptibility to therapeutic attack.

10. NIMH-SIRB-60
SOCIAL TONEDA

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED - PERMANENT PROF	BUDGETED - PERMANENT OTHER	BUDGETED - PERMANENT TOTAL	BUDGETED - TEMP PROF	BUDGETED - TEMP OTHER	BUDGETED - TEMP TOTAL	PROFESSIONAL YEARS
FY 1955	58,200	5	4	9	4 1/3	4	8 1/3	
FY 1956	60,100	5	4	9	5	4	9	

12. BUDGET ACTIVITY:

RESEARCH — ☒ DEMONSTRATION ☐

ACTION & APPROVAL ☐ TRAINING & EDUCATION ☐

13. IDENTIFY ANY COOPERATIVE TIES OF THIS FIELD SERVICE, BY OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR WORK PLANNED BY SERVICE 1955-1956. IF COOPERATING UNIT IS WITHIN NIH INDICATE SPECIAL ROUTING

Section on Endocrinology, Lab, NIAMD- SIRB-4,7
Pathologic Anatomy Department, NC

14. IF THIS PROJECT RESULTED, DURING 1954, IN A SPECIAL PUBLICATION IN THE FIELD HEALTH SERVICE (WITHOUT EXPENDITURE OF PERSONNEL, FACILITIES OR FUNDS), INDICATE SUCH RESEARCH: (BY GRANT NO(S) IN NIMH NOA)

(Fellner, Bureksono) NIMH-

15. NIH(D)-62121-60
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Bangle, R. Jr., and Alford, W. C.: The chemical basis of the periodic acid Schiff reaction of collagen fibers with reference to periodate compounds by collagen and by insulin. J. Histochem. & Cytochem. 2: 62-76, 1954.

Emmart, E. W., and Longley, J. B.: The reactivation of heat-inactivated hyaluronidase. J. Gen. Physiol. 37: 361-371, 1954.

Bangle, R. Jr.: The periodic acid-Schiff stain. Am. J. Clin. Path. 24: 179-185, 1954.

Fisher, E. R., and Lillie, R. D.: The effect of methylation on basophilia. J. Histochem. & Cytochem. 2: 41-47, 1954.

Lillie, R. D., Bangle, R., and Fisher, E. R.: Metachromatic basophilia of keratin after oxidation-cleavage of disulfide bonds. J. Histochem. & Cytochem. 2: 95-104, 1954.

Lillie, R. D.: Argentaffin and ASTRAT reactions after periodic acid oxidation and aldehyde blocking reactions. J. Histochem. & Cytochem. 2: 427-436, 1954.

Bangle, R., Jr.: Gomori's permanganate-hematoxylin stain I. Mordant-chromate and staining properties of the dye. J. Histochem. & Cytochem. 2: 251-257, 1954.

Lillie, R. D., and Bangle, R., Jr.: The paracetic acid Schiff reaction of hair cortex. J. Histochem. & Cytochem. 2: 300-311, 1954.

Lillie, R. D.: Spurious publication dates. Science, 120: 14, 1954.

Warmbier, W., Gindrup, D. E., Stephens, J., Lillie, R.D., Feldmann, G.: Corneal involvement with advanced periventricular calcification in generalized cytomegalic inclusion disease in the newborn. J. Pediatr. 44: 562-585, 1954.

Bahn, R. C.: Recent progress in hormone research. Science, 119: 744, 1954.

Longley, J. B., and Fisher, E. R.: Alkaline phosphatase and the periodic acid Schiff reaction in the proximal tubule of the vertebrate kidney. A study in segmental differentiation. Anat. Rec. 120: 1-17, 1954.

Lillie, R.D. and Henson, J.F. Creon: Xylene-cellulose caprate as a histologic mounting medium of low refractive index. Stain Technol. (In press)

16. PUBLICATIONS - Continued:

Longley, J. B., and Finney, R. L.: A bibliography of basis for computing the Bessel function in young stars. J. Soil. Comp. Physics. (In press)

17. LIST TITLES AND AUTHORS OF PAPERS, RELATED TO THIS PROJECT, PUBLISHED DURING YEAR 1953:

None

1. National Institute of Arthritis and Metabolic Diseases

2. Pathology and Histochemistry LABORATORY

3. Pathologic Anatomy SECTION

4. Botswana INDIVIDUAL

5. NIAMD-62LP2-21 SERIAL NUMBER

6. PROJECT TITLE: a. Study of the possible pathologic expression of [illegible] hypersensitivity in experimental autoimmunoses.

b. Renal lesions induced by spermine and related polyamines.

c. Human pathology (diagnostic - research).

d. Pathologic studies of endocrine glands. (Completed in fiscal year 1958).

7. L. L. Ashbaugh
PRINCIPAL INVESTIGATOR

8. Dean Lagunoff
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

a. Immunity and hypersensitivity in autoimmunoses.

Objectives: To determine whether or not immunity or hypersensitivity develops in experimental autoimmunoses.

Methods Employed: Presence of mice is essential. After mating interesting mice are treated or kill the embryos. The experimental treatment schedule is necessary a varying number of mice in different groups of mice. In addition to clinical evaluation, pathologic [illegible] tissue and cell will be evaluated by [illegible]

Major Findings: Data being evaluated at present.

significance to NIAMD Research: There is disagreement as to the proper "dose" schedule in cortisol treatment of this disease; some therapists even claiming this treatment does more harm than good. Data on possible immune-hypersensitivity mechanism would be helpful in rationalizing therapy.

Proposed Course of Project: Dependent on results of this preliminary [illegible]

9. PROJECT DESCRIPTION: Continued

b. Renal lesions induced by spermine and related substances.

Objective: To determine whether or not the administered substance or a metabolic product is responsible for renal lesions.

Methods Employed: Administration of chemical by routes primarily by-passing organs probably involved in metabolism; also administration of "degraded" product.

Major Findings: None - methods still being developed.

Significance to NIAMD Research: Spermine is normally present in certain human tissues. A knowledge of the possible effect of this substance and its metabolic products on the kidney would seem of particular importance in renal disease.

Proposed Course of Project: Refinement of methods (other routes of administration, etc.) to elucidate effects of metabolic products of spermine.

c. Human pathology - diagnostic, research.

Various members of this and other sections of the Laboratory of Pathology and Biochemistry participate in the study of human tissues received from various Federal hospitals. Although a diagnostic service is rendered, the material is used for various research purposes by many members of the laboratory. This includes cooperation in Renal Disease Research Program - unbalanced myelitis study.

10. [illegible]
[illegible]

11. BUDGET DATA:

	SCIENTIFIC EXPENDITURES	PROFESSIONAL POSITIONS			MAN YEARS			PATIENT DAYS
		FULL	PART	TOTAL	FULL	PART	TOTAL	
FY 1955	20,400	1	1	1½	1½	5/6	1 1/3	
FY 1956	20,400	1	1	1½	1½	5/6	1 1/3	

12. OTHER ENTITIES:

GRANTEE:	☐	CONTRACTOR	☐
OTHER (Specify)	☐	TECHNICAL ASSISTANCE	☐

13. [illegible] ARE COOPERATING WITH OF THE PUBLIC HEALTH SERVICE IN THESE NEGOTIATIONS, PROVIDING SPACE, FACILITIES, OR PERSONNEL FOR WORK UNDERWAY IN FISCAL 1955 OR 1956. IF COOPERATING, WRITE IN VETERAN OR ASSOCIATE SERIAL NO(S).

Laboratory of Tropical Diseases, NIH
Section on Pharmacology, NIH, [illegible]

14. IF THIS PROJECT RECEIVES, OR EXPECTS, TO RECEIVE ANIMALS OBTAINED FROM DEALERS IN THE PUBLIC HEALTH SERVICE SUPPLY SOURCE (LIVESTOCK OR ANIMALS PURCHASED WITH FUNDS), EXPLAIN SUCH RESEARCH. (SEE SERIAL NO(S). IF ENTERED BELOW)

a. Project on schistosomiasis is a cooperative one with Dr. [illegible] of National Cancer Chemotherapy Institute.

b. The principal investigators in this specific project are Drs. Rosenthal and Colin Tator.

15. NIMH-C2L2S-61
SERIES NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS WHICH THIS PROJECT HAS PRODUCED DURING CALENDAR YEAR 1954:

Bisher, S. N., and Rosenthal, S. M.: Pathology and pathogenesis of [illegible]-induced renal disease. Arch. Path. 57: 240-253, March 1954.

Fisher, E. W., and Fisher, E.: Glomerular lipoidosis in the dog. Am. J. Vet. Res. 15: 295-306, 1954.

David, J. C., Howell, D. S., Lequear, C. L., and Peirce II, E. C.: Renal hemodynamic function, electrolyte metabolism and water exchange in adrenalectomized-hypophysectomized dogs. Am. J. Physiol. [illegible]: [illegible], [illegible].

Bangle, R. Jr., and Sawyer, C. H.: Giant hypertrophy of the lateral thoracic nuclei associated with recurrent laryngeal section. Am. J. Path. 30: [illegible], 1954.

The influence of the central nervous system on metabolism and endocrine activity as based on transections of the brain stem in dogs. Evelyn Hickman, Theodore Knowlton, William T. Dumas, E. V. Nelson, Carl L. Lequear, Carlo Sala, Hardy, and Webb Haymaker. (Accepted for publication by Acta Neuroveg[illegible], [illegible].

Neurosecretory pathways between the hypothalamic paraventricular nucleus and the neurohypophysis. (Accepted for publication in Journal of Comparative Neurology, C. L. Lequear).

17. LIST TITLES AND NAMES OF PERSONS RELATIVE TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

P.C. - 1

Contract of DHEW Research Activities

Project Description Sheet

MIAMI
INSTITUTE

5. PATHOLOGY AND HISTOCHEMISTRY
LABORATORY

Pathologic Anatomy
SECTION

4. [illegible]
DEGREE(S) (IF OTHER THAN MEDICAL

5. [illegible]
Contract No.

Project A: High Altitude; Project B: Production of Experimental Arterial Hypertension
PROJECT TITLE

and Chronic Valvular Defromities; Project C: Dietary Cholelithiasis in Mice;

Project D: Pathology of Malaria in Animals; Project E: Toxicity of Insulin and T[illegible]

B. Hirsch
PRINCIPAL INVESTIGATOR

OTHER INVESTIGATORS

PROJECT DESCRIPTION:

Project A - Rats Livernale

Objectives: To study effects of chronic hypoxia exposure to simulated high altitude on various species of mice and rats (Swiss) animals.

Methods Employed: Animals are exposed several hours daily in a low pressure chamber to a simulated altitude of 25,000 feet.

Major Findings: Altitude rats develop, in addition to polycythemia, marked cardiac and cardiac hypertrophy, cardiac regurgitation, renal infarcts, and damage to the testes and other organs. Similar changes, varying according to individual species and strains of animals, were noted in mutiple studies.

Significance: Our findings may be of significance to those concerned with aviation medicine, health at high altitude inhabitants, and laboratory investigation of cardiovascular, endocrine and other metabolic disorders.

Proposed Course of Project: Rats exposed to high altitude will be used in study of experimental endocarditis (Proj. B).

VAID-0-2-3-82
PHS-1 NO.

Project B

Production of Experimental Bacterial Endocarditis and Chronic Valvular Deformities

Objectives: To produce endocarditis and chronic valvular deformities, to determine factors predisposing to endocarditis, to study the development of the lesions and causes of treatment failures, and to test in vivo the effectiveness of various forms of therapy.

Methods Employed: Animals acclimatized to high altitude and ground level conditions were inoculated intravenously with various bacteria. Some received antibiotic therapy. Pathologic studies were made at intervals after inoculation.

Major Findings and Significance: Studies of altitude rats inoculated with viridans streptococci and treated with penicillin revealed the continued persistence of bacteria in endothelial cells and macrophages in valvular vegetations and in necrotic and suppurative foci in the heart and kidneys; this may help explain some of the causes of treatment failures and the need for prolonged treatment in human endocarditis. Some rats recovering after therapy developed valvular deformities similar to aortic mitral and other chronic valvular lesions seen in human cardiac disorders.

Endocarditis was produced in altitude rats by intravenous injections of Haemophilus parainfluenzae. Similar injections failed to produce endocarditis in ground level rats even when cortisone was administered indicating that adrenal hyperactivity is not the primary factor predisposing to bacterial endocarditis. Evidence was found that concomitant hypoxia and polycythemia are necessary predisposing factors.

Endocarditis was readily induced in altitude rats by injecting cultures of Streptococcus, Staphylococcus, and Hemophilus isolated from clinical cases and may be useful in studying the pathogenesis and the therapy in vivo of endocarditis due to these organisms.

Proposed Course of Project: The susceptibility to endocarditis of rats conditioned to high altitude is under investigation. (If acute and chronic endocardial lesions can be produced in a large animal like the dog, as they have been produced in the rat, it will greatly facilitate surgical and physiological studies on heart disease and associated metabolic disorders.)

Project C : Dietary Calcification in Mice

Objectives: To determine factors causing calcified lesions in heart, aorta, arteries and lungs of C3H mice fed a purified low protein diet.

Methods Employed: Various supplements are added to diet and resultant change in incidence and degree of calcification is determined histologically.

Major Findings: Calcification is greatly lessened by increasing protein and by certain supplements.

[illegible]
[illegible] 6D.

Significance: May shed light on pathogenesis of certain forms of [illegible] relevance and on possible immunological applications.

Proposed Course of Project: Further modifications of diet to be followed by [illegible] levels.

Project D: Pathology of Malaria in Animals

Objectives: To determine cause of death and difference in survival time in different strains of mice.

Methods Employed: Animals are studied histologically at intervals after inoculation with Plasmodium vinckei.

Major Findings: Pathologic changes develop more rapidly in inbred Balb mice (rarely survive 8 days) than in ddY mice (usually survive 2 weeks).

Significance: May elucidate factors affecting resistance to malaria in man.

Proposed Course of Project: Different strains of mice with different survival after malaria inoculation will be studied histologically. In collaboration with Dr. Altland, the influence of altitude polycythemia on length of survival of mice inoculated with P. vinckei is under investigation.

Project E: Toxicity of Iodides and Iodates

Objectives: To determine possible health hazards in use of iodides and iodates, particularly for prevention of goiter.

Methods Employed: Animals are examined histologically at various periods after administration of iodides and iodates by various routes.

Major Findings: Iodates cause damage to parietal cells of stomach and to testes.

Significance: May be useful tool in studying pathogenesis of certain ova and stomach disorders.

Proposed Course of Project: Studies will be continued to determine safe [illegible] limits.

Other Projects: From time to time consultation is given to or tissues are provided for various other professional workers at NIH. For example, tissues of animals infected with trypanosomiasis are being studied for Mrs. P. E. Coles.

[illegible]

1. [illegible]

2. [illegible]

	[illegible]	[illegible]			[illegible]			
	[illegible]	PHS	OTHER	TOTAL	PHS	OTHER	TOTAL	
FY 1955	[illegible]	1	1	2	1	1.5	2.5	
FY 1956	[illegible]	1	1	2	1	1.5	2.5	

3. [illegible]

[illegible] [X] [illegible] [ ]

[illegible] [ ] [illegible] [ ]

4. [illegible]
[illegible]
[illegible]
[illegible]
[illegible]
[illegible]

5. [illegible]

Page - 1

Information for Research Projects

Annual Progress Report

1. USAMD
INSTITUTION

2. Pathology and Bacteriology
DEPARTMENT

3.

Pathological Anatomy
SECTION

4.
(Complete for Grant Only if necessary)

5.

Study of Mechanisms Involved in Intercellular Diseases
PROJECT TITLE

E. H. Layton
PRINCIPAL INVESTIGATOR

OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: The objective of this project is to study the causes of intercellularly induced infections, emphasizing bacteriologic, immunologic, and chemical methods of investigation, in order to elucidate some of the factors influencing host-parasite relationships.

Methods Employed:

(a) Animals are injected and studied following the principles in Public Health Service publications and other literature. Specialized cultural methods are employed in cases of atypical acute infection, to recover the atypic microorganism. Animals that have been sacrificed, and from normal animals, are isolated and characterized.

(b) Pathological studies are carried out on those tissue specimens of interest to the investigation, to determine whether noticeable vascular changes in blood vessels or brain occur which influence localization of pathogens in cerebrospinal

Major Findings:

(a) Several strains of Streptobacillus monilifermis have been isolated from a variety of atypical human infections, as well as from cases of infectious rabbit. These strains have caused septic and chronic lesions when injected into rabbits, guinea pigs, and the organisms were recovered on cultures of tissues. Infected animals also showed similar lesions occasionally, and reciprocal studies have revealed an exceptionally high incidence of hemorrhage-producing infections with this microorganism in laboratory animals.

(b) No macroscopic or microscopic changes were found in either sex or both of mice injected intramuscularly with purposely graded, although the incidence of paralysis in injected limb was increased when mice were infected twice with poliomyelitis virus.

Significance to NIAID Research:

(a) Streptobacillus moniliformis occurs in hitherto unsuspected areas of human infection, including upper respiratory disease. The natural reservoir of this microorganism in some laboratory animals is known, while no natural studies with the organism. Lesions may still be produced by injection of large doses into these animals. Great care must be exercised to exclude the possibility of natural infection with this organism.

(b) Absence of marked nervous system damage and presence of Wallerian type changes in mice injected with peritonitis causing organisms may be indicative of paralysis might be the result of accumulation of toxin in a non-specific inflammatory focus. This would imply the possibility of a neurotoxic organism of the poliomyelitis virus.

Proposed Course of Project:

(a) Search for a suitable small experimental animal for studies with Streptobacillus moniliformis, by careful cultural screening, etc., to find an animal that does not normally carry the organism and is highly susceptible to infection with it. Study the pathogenesis of infection with this organism in this animal, and evaluate the interrelation or similarity of the various strains which have been isolated from human and animal infections.

Continue to screen human infections primarily for this microorganism and secure these strains in animals.

Employ immunological techniques to supplement cultural laboratory procedures for the identification of these strains. These will include agglutination-lysis methods, as well as complement fixation techniques employing cytosols of live and killed bacterial suspensions by blood laboratory procedures according to recently developed procedures.

(b) Filtration of poliomyelitis virus in filtrate of animals infected with organisms of local inflammation, in order to detect possible concentration of virus in a non-specific inflammatory focus.

4. NIAMD-62182-63
SERIAL NO.

5. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PAYMENT DATE
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	11,760	1	½	1½	1	½	1½	
FY 1956	11,709	1	½	1½	1	½	1½	

6. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TRAINING [ ]

7. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE [illegible] PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN [illegible] IF COOPERATING UNIT IS WITHIN NIH, INDICATE SERIAL NO(S) (ITEM 4)

Laboratory of Infectious Diseases: LID
Section on Bacterial and Mycotic Diseases
Section on Basic Studies

8. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH [illegible] IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

i.

[illegible]

[illegible]

j. NIAMD-62122-63

k. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR [illegible]

l. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1964:

10. [illegible]

11. BUDGET DATA:

	Estimated Expenditures	Proposed Federal Aid			Applicant Share			Program Income
		Basic	Matching	Total	Basic	Matching	Total	
FY 1955	$2,400	1/3	0	1/3	2/3	1 1/3	2	
FY 1956	$4,800	1/3	1/3	2/3	2/3	1 1/3	2	

12. BUDGET NOTATIONS:

[illegible] ☒ [illegible] ☐

[illegible] ☐ [illegible] ☐

13. [illegible]

[illegible]

14. [illegible]

None

15. [illegible]
Social Studies

16. [illegible]
1954

None

17. [illegible]
None

1. National Institute of Arthritis and Metabolic Diseases
DIVISION

2. Pathology and Biochemistry
LABORATORY

3. Comparative Pathology and Parasitology
SECTION

4. Outbreaks
ESCTION

5. Grant - 5:R01-AM-
Public Health

6. Naturally Occurring Diseases of Laboratory Animals
PROJECT TITLE

7. Robert P. Hubschman
PRINCIPAL INVESTIGATOR

8. Fletcher F. Williams, Jr.
OTHER INVESTIGATOR

9. PROJECT DESCRIPTION:

Determination of the incidence and cause of the naturally occurring diseases in laboratory animals and development of methods for the control and treatment of these diseases.

Objectives: The objectives of the project are to develop techniques, insofar as approved, Pilgrim-free animals for studies of the natural derivation of healthy conduct research into parasitic, bacterial, viral, mycotic, and metabolic diseases to enable investigators to distinguish between lesions produced experimentally from those produced by the naturally occurring diseases in the animals; to develop effective methods for the control or prevention of these diseases; and to develop techniques for the early recognition of an outbreak of disease in the animal colonies.

Methods Employed: The efficacy of control of parasitic diseases is accomplished by painting various external membranes of the body, cages and racks for metals control; by testing of laboratory animals for insecticidal and by admixture of antihelmintics in the diet. The efficacy of sanitation and of care of laboratory animals and the efficacy of diagnostic methods and tests is measured. Autopsy of sick, diseased and aged animals is conducted with parasitological, bacteriological and histopathological examinations to determine incidence and cause of disease.

Major Findings: The major findings of this project during the past year have been (1) the use of a saturated solution of sulfamethazine in drinking water of rabbits for the control of coccidiosis, (2) the identification of some of the common helminth eggs and protozoa of laboratory animals, and the publication of pamphlet with photomicrographs of the characteristic eggs and protozoa, and (3) the incidence and pathologic findings of histoplasmosis in 3 colonies of 50 cats.

Significance to Field Research: (1) The elimination of roundworms in experimental rabbits makes the experimental results in liver, nutrition, and radiation studies more reliable and trustworthy. (2) The photomicrographs of helminths and protozoa make the identification of the common helminths and protozoa infections of laboratory animals quick and easy. (3) The minor importance of dogs and cats in the transmission of histoplasmosis to man and animals has been reported.

Proposed Course of Projects: A considerable portion of the next calendar year will be devoted to the control, treatment, and elimination of diseases from the laboratory animals in the CDC animal colonies; to determine incidence of Leptospira spp. in the laboratory animals; and to determine the incidence of mycotic diseases in the laboratory animals.

10. [illegible]

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	FEDERAL FUNDS			NON-FEDERAL FUNDS			PROGRAM INCOME
		(a)	(b)	(c)	(d)	(e)	(f)	
FY 1955	89,500	2	2½	4½	1	½	1½	
FY 1956	49,500	2	2½	4½	1	½	1½	

12. BUDGET ACTIVITIES:

[illegible] ☐ [illegible] ☐

[illegible] ☐ [illegible] ☐

13. [illegible]

None

14. [illegible]

None

15. NIMH - 00183-03

16. [illegible] Annual [illegible] Conference, [illegible] 1954:

Ausley, Donald A., Robert F. Hagenmaier, and Charles W. Lindsay. [illegible] Periodontal Studies of Vitro Cake and Pilot Caps from Lactose Sugar. [illegible] Jr. Dent. Res., 25, 85-111; illegible 1954.

Hagenmaier, Robert F. and Robert F. Steinmann. Inhibition of Enterococcus [illegible] and Results of Laboratorial Investigations. Jour. [illegible], Volume September 1954.

Hagenmaier, Robert F., [illegible], and Robert F. Steinmann. [illegible] of Electrolytes Excreted and Urea. Jour. [illegible], 25:53, October 1954.

Steinmann, Robert F., Clarence H. Gilliam, Jr., and Robert F. Hagenmaier. Contributions to the Physiology and a Discussion of the Evolution Laughs. J. Gen. Psy. Res. Assoc., [illegible], 250-253, October 1954.

Hagenmaier, Charles C., [illegible], Illinois, Mr., Robert F. Steinmann, and [illegible]. The Epidemiology of Complete Dentures in [illegible] J. Ret. Career Deal. [illegible] County. [illegible]

Hagenmaier, Robert F., Jacob F. Steinmann, and Robert F. Steinmann. [illegible] Fitness in Retirees [illegible] Jour. Gerontology [illegible] Research. [In press].

Gilliam, Jr., Robert F. Hagenmaier, and Carlton F. Steinmann. [illegible] and Effectiveness of [illegible] [illegible] [illegible] Psychology and Personality. [In press]

17. [illegible] and Studies of [illegible] [illegible] [illegible] [illegible] Mind [illegible]

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pathology and Biochemistry
LABORATORY

3. Comparative Pathology and Nutrition
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62123-56
ANIMAL NUMBER

6. Study of Liver Cell Mitochondria in Relation to Dietary Procedures
PROJECT TITLE

7. G.L. Hite
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Study of the mitochondria of liver cells under various dietary conditions.

Objectives: To learn something of mitochondrial changes occurring in cellular response to variations in nutrients in the diet.

Major Findings: The degenerative changes in liver cells in rats on deficient diets are the earliest recognizable alterations in the liver cell and degenerative changes in mitochondria.

Significance to NIAMD research: [illegible] While known field of investigation of considerable promise.

Proposed Course of Project: An elaborate effort, by available means, to [illegible] shape, number, size and forms of mitochondria as related to dietary variants such as [illegible] lipids, toxic agents etc.

10. 31420 - 6811-65
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	REQUIRED PERSONNEL			NEW FUNDS			CHANGE FROM
		PHS*	OTHER	TOTAL	PHS*	OTHER	TOTAL	
FY 1955	$1,100	1	½	1½	1	½	1½	
FY 1956	$1,100	1	½	1½	1	½	1½	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDED FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL 1955 OR 1956. IF COOPERATING UNIT OR OTHER ORGANIZATION IS NOT LISTED, SPECIFY:

Section on Biochemistry and Physiology of Infection, LIH 31420 - 6811-C

14. IF THIS PROJECT DUPLICATES, COMPLEMENTS, OR PARALLELS ANOTHER PROJECT CURRENTLY IN THE PUBLIC HEALTH SERVICE (REGARDLESS OF SOURCE OF FUNDS), IDENTIFY SUCH PROJECT (BY SERIAL NO. (S) IF KNOWN FOR):

None

15. NIAMD - 60231-66
SERIN, Nathan

16. LIST NUMBERS (FROM ONE) OF PUBLICATIONS LISTED UNDER DUTIES ON PREVIOUS PAGE
1954:

Fitz, G.L. : The Pathology of Dietary Liver Necrosis. Annals N.Y. Acad. Sci., 57, 183-8 (1954)

17. LIST HONORS AND AWARDS TO BE RECEIVED RELATING TO DUTIES ON PREVIOUS PAGE
1954:

None

1. National Institutes of Arthritis and Metabolic Diseases
INSTITUTE

2. Pathology and Hitochemistry
LABORATORY

3. Comparative Pathology and Hematology
SECTION

4. Barbados
LOCATION

5. NIAMD - 62123-3Y
SPECIAL NUMBER

6. Studies on Regulation of Hemopoiesis
PROJECT TITLE

7. George Brecher and Frederick Stohlman, Jr.
PRINCIPAL INVESTIGATORS

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Transfusion of separated platelets and white blood cells in replacement therapy in aplastic anemia.

Objectives: Identification and characterization of substances capable of stimulating erythropoiesis.

Methods Employed: Bone marrow aplasia is induced by irradiation. Viable platelets and white blood cells are separated from freshly drawn blood by methods developed in this laboratory and concentrated suspensions transfused into compatible recipient dogs. Measurement of erythropoiesis involves measurement of radio-iron incorporation into red cells, radio-iron clearance, survival studies of red blood cells as well as the study of stimulators and inhibitors of hemopoiesis.

Major Findings: (1) In addition to actual blood loss necessary to thrombocytopenia, anemia in platelet deficient dogs is observed as continued escape of red cells from small vessels. The red cells are absorbed by lymphatics and returned to the general circulation but their life span is reduced, presumable due to damage during their extravascular cycle. This potential cause of shortened red cell survival has not been previously realized and is probably operative in severe thrombocytopenia of any type. (2) While measuring red cell survival by tagging cells with radiochromium it was found that changing chromium loss is a very sensitive indicator of red cell damage.

[illegible]

10. NIMH - 62121-67
SOCIAL WORKER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	SUGGESTED PERSONNEL			SRS USE			[illegible]
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	20,600	1	2 1/3	3 1/3	1	2 1/3	3 1/3	
FY 1956	20,600	1	2 1/3	3 1/3	1	2 1/3	3 1/3	

12. PROJECT ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

SERVICE & TRAINING [ ] TECHNICAL ASSISTANCE [ ]

13. [illegible] ARE ASSOCIATED WITH THE PUBLIC HEALTH SERVICE SERVICE [illegible] CLINICS, INCLUDING FILMS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL 1955 OR 1956? IF COORDINATION WILL BE NEEDED GIVE DETAILS BELOW OR INDICATE SERIAL NO. OF

Rural Medical Research Institute

14. IF THIS PROJECT INCLUDES SCHOLARSHIPS OR TRAINING ASSISTANCE IN THE PUBLIC HEALTH SERVICE (WITHOUT LIMITATION TO [illegible] PROGRAMS), IDENTIFY SUCH ASSISTANCE: (BY SERIAL NO. (6) IN ITEM 10)

None

15. NIAMD - 02413-07
SERIAL NUMBER

16. LIST PUBLICATIONS ARISING FROM THIS PROJECT DURING THE PAST YEAR. INDICATE IN PRESS
1954.

Drescher, D., F. Stohlman, Jr., and A.S. Gordon. Shortened Red Cell Survival
in Experimental Thrombocytopenia Induced by Toxoid Injection.
Rouxo d'Hematologie.

17. LIST HONORS AND AWARDS RECEIVED DURING THE PAST YEAR OR ANTICIPATED DURING THE
CY 1954:

None

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pathology and Histochemistry
LABORATORY

3. Comparative Pathology and Parasitology
SECTION

4. Bethesda
LOCATION

5. MIAMD-GMIL3-58
SERIAL NUMBER

6. Comparative pathology of virus diseases
PROJECT TITLE

7. Dr. Ladd M. Lourie
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

a. A study of the pathology of central nervous system virus infections

Objective: On a comparative diagnostic basis the study of various isolated nervous system disorders for evaluation as to whether it is of a virus origin or not. Some animals that show clinical signs of a CNS disorder do not always have a diagnosable pathological virus lesion.

Methods Employed: Standard pathological methods

b. Cooperative study of a technic of virus purification (Newcastle Disease Virus)

Objectives: To see if the use of cellulose filtration combined with an antigen antibody complex will result in virus purification after ultracentrifugation.

Methods Employed: Ultracentrifugation of allantoic fluid Newcastle Disease preparations.

Filtration using powdered cellulose columns coated with anti-allantoic fluid protein rabbit sera and re-evaluating the purified virus by means of LD-50 and virus hemagglutination tests.

c. Monkey safety tests of the Salk polio vaccine

Objectives: Examination of brain and spinal cord tissue sections from inoculated Rhesus and Cynomolgous monkeys for evidence of live virus in the Salk polio vaccine.

9. PROJECT DESCRIPTION - Continued

d. A study of the pathogenesis of [illegible] and a study of the skeletal muscle lesion

Objectives: A study of muscle lesions at short periods in [illegible] which are beginning from 12 hours to 20 days.

Methods Employed: Using standard preparations and special stains [illegible] differentiation of, and much production by, the muscle

Ref Ex - 8
December 1956

Address of NIH Grantee Organization

Cold Spring Harbor, New York

10. NIAMD-6212-05
SOCIAL SECURITY

11. BUDGET DATA:

	RECOMMENDED EXPENDITURES	DIRECTED POSITIONS PROF	DIRECTED POSITIONS OTHER	DIRECTED POSITIONS TOTAL	MAN YEARS PROF	MAN YEARS OTHER	MAN YEARS TOTAL	PRIORITY RATING
FY 1955	11,300	1	1/3	1 1/3	1	1/3	1 1/3	
FY 1956	11,300	1	1/3	1 1/3	1	1/3	1 1/3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL 1955 OR 1956. IF COOPERATING UNIT IS WITHIN NIH INDICATE SOCIAL SECURITY NO(S).

Section on Physical Biochemistry, LPB, NIAMD-6612C-
Section on Pathologic Anatomy, LPB, NIAMD-6612C-
Section on Carbohydrates, LC, NIAMD-6211B

14. IF THIS PROJECT TERMINATES, WITHDRAWALS, OR FUNDING CHANGES WOULD SIGNIFICANTLY AFFECT THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), INDICATE SUCH PERSON: (IF SOCIAL SECURITY IS OTHER THAN

None

Patents, Awards, and Publications Sheet

15. NIAMD-G2128-60
Senate Bureau

16. List Publications which you consider to be the most significant of those listed during the year 1954:

None

17. List Honors and Awards to personnel of your group in this project during the year 1954:

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pathology and Histochemistry
LABORATORY

3. Comparative Pathology and Geriatrics
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62123-69
SERIAL NUMBER

6. Degenerative Joint Disease in Small Laboratory Animals
PROJECT TITLE

7. Leon Sokoloff
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The object of this project is to determine factors influencing development of degenerative joint diseases in small laboratory animals.

Methods Employed: Chronologic, and to a lesser extent roentgenologic examination of the joints of various small animals in the categories are being made: 1. spontaneously aged and 2. experimentally altered conditions.

Major Findings: A. Because degenerative joint disease is largely a manifestation of senescence (a process which sets in at the end of maturity) much of the effort of the last year has been devoted to developing a colony of old animals. To date, approximately 1500 rats and mice comprising 13 strains of mice, 11 of rats, as well as hamsters and guinea pigs have been obtained. Approximately half of these have been harvested to date. Conclusions concerning the natural history of articular degeneration are necessarily tentative at the present time. A pattern of spontaneous cystic degeneration of articular cartilage has been found in rats but this species is strikingly resistant to development of osteoarthritis unlike mice and hamsters. B. Osteoarthritis has been found to develop in a proportion of old obese rats (Dr. Nickelsen), and rats exposed to conditions simulating high altitude (Dr. Allard). Negative results have been obtained in thyro-hypophysectomized rats (Dr. Snow), those on cariogenic-producing diets (Dr. Daft) or those treated with Growth Hormone for 30 days. C. A variety of undescribed spontaneous disorders of the animals have been observed (congenital and acquired) that will be of interest

to geneticists and workers in the field of experimental arthritis. An example of the former is isolated absence of the secondary center of ossification in the capital epiphysis of the femur. Examples of latter include cellulitis and actinomycosis of the paws.

Significance to NIAMD Research: Degenerative osteoarthritis is by common and economically most destructive form of human joint disease from the point of view of public health. It has, with one outstanding exception, not been the subject of systematic experimental study in recent years. This reflects a popular assumption that the disorder is an inevitable manifestation of old age. Although recognized to occur in virtually all bulky animals, rodents have been considered immune until recently. The results in the rodents encourage the hope that prophylactic measures, if not inhibiting agents, may be devised for the human disorder.

Proposed Course of Project: 1. Distribution of degenerative changes in the various species is being determined: a. to determine joints most suitable for study in this field. b. to compare effect of posture on development in these species compared to man. 2. Radiologic methods for diagnosis are being evaluated with pathologic preparations. 3. Genetic studies are to be carried out with Dr. Jay in an attempt to produce high arthritis strains. Almost all the animals are from the inbred colony, so that their genetic background is known. 4. Biochemical studies will attempt to define similarities and differences from the human disorder. Chemical alterations in the matrix of the cartilage that allow the cartilage to come apart may be divulged by appropriate methods. 5. Experimental production of osteoarthritis will be pursued: a. multifactorial: a. Dr. Nicholas: effects of obesity of various kinds, exercise, forced exercise in rats. b. Dr. Aldred: high altitude exposure in hamsters. c. Independently, it is planned to determine the effects of thyroxine and selenium on the joints.

10. NE/MD - 0243-69
SOCIAL MEDICINE

11. BUDGET DATA

	DOLLARS (IN THOUSANDS)	PROFESSIONAL POSITIONS			MAN YEARS			FOREIGN CURR.
	EXPENDITURES	PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	13,600	1	2 1/3	3 1/3	1	2 1/3	3 1/3	
FY 1956	14,600	1	2 1/3	3 1/3	1	2 1/3	3 1/3	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

DEMONSTRATION [ ] TRAINING [ ]

13. DESCRIBE THE COORDINATED EFFORT OF THE PUBLIC HEALTH SERVICE, AS APPROPRIATE, IN OTHER ORGANIZATIONS, PROVIDED FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN 1955 OR 1956: (IF NONE, SO STATE.)

None

14. IF THIS PROJECT REQUIRES, SUBSEQUENTLY, OR CONTINUES ASSISTANCE PREVIOUSLY GIVEN BY THE PUBLIC HEALTH SERVICE (GRANTS, LOANS, OR GRANTS OF FEDERAL PERSONNEL OR FUNDS), INDICATE SUCH ASSISTANCE & GIVE CASE NO. (IF IT APPLIES):

None

N.I.H. - 1
December 1965

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pharmacology and Toxicology
LABORATORY

3. Pharmacology
SECTION

4. Bethesda
LOCATION

5. AM-05213-10
PROJECT NUMBER

6. The Biosynthesis of the mucopolysaccharides and glucuronides and cellular localization of hyaluronidase

7. Jack L. Strominger
PRINCIPAL INVESTIGATOR

8. R. W. Brown
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To elucidate the mechanism of biosynthesis of the mucopolysaccharides and glucuronides. By the use of fluorescein labeled antibody to streptococcal hyaluronidase to determine the cellular localization of this enzyme in mammalian tissues.

Major Findings: Chromatographic methods were developed for the isolation of uridine nucleotides. High concentrations were found in the bovine oviduct, and characterization of some of these compounds revealed that they were uridine pyrophosphate conjugated with (a) N-acetyl glucosamine and (b) N-acetyl galactosamine sulfate. Since the oviduct is important in the synthesis of glycoproteins and mucopolysaccharides, these findings suggest a biosynthetic pathway.

An enzyme was obtained from liver which catalyzed uridine diphosphate glucose to uridine diphosphate glucuronic acid, thus demonstrating the pathway of formation of the glucuronates. The enzyme has been purified 100 fold.

Using the method of labeling antibody by conjugation to a fluorescent dye, antibody against streptococcal hyaluronidase has been produced in rabbits, and the serum labeled in this way. Equipment for microscopic demonstration is being assembled, and after injection of the antigen in mice, tissues will be treated with the fluorescent antibody and the localization studied histologically. It has also been found that hyaluronidase, inactivated by heat, becomes spontaneously reactivated on standing.

9. PROJECT DESCRIPTION - Continued

Proposed Course of Project: The [illegible] of Dr. Strominger to [illegible] Kaelin Fellowship presents [illegible] plans for biochemical studies. The histochemical [illegible] injected [illegible] will be continued.

Budget Bureau No. 68-R1

Analysis of NIH Program Activities

Project Data Sheet

1a. NIAID-Seigel-70
Serial Number

1b. Budget Data:

	Estimated Expenditures	Professional Positions			Staff Years			Personnel Costs
		Grad	Other		Grad	Other	Total	
FY 1957	23,300	8	13	21	8	13	21	
FY 1958	25,300	8	13	21	8	13	21	

1c. Method Category:

Research ☒ Contract ☐
Service & Approval ☒ Grant-in-Aid ☐

1d. Identify the cooperating units of the Public Health Service, the other agencies, providing funds, facilities, or personnel and the amount to be used in 1957 or 1958. If cooperating unit is within the Institute, specify.

Code #DCT = 55
Section on Biochemistry, IPH, (NIAID- 62121-55)
Section on Enzymes and Cellular Biochemistry, IPH, (NIAID- [illegible])
Section on Oxidases and Cellular Biochemistry, IPH, (NIAID- [illegible])

1f. Is this project research, surveillance, or training? Indicate its relation to the Public Health Service (without interchange of personnel, facilities or funds), identify such research. (If Serial No.(s) is given, it is sufficient.)

None

15. NIAMD-5218-76

16. [illegible]

Strominger, J. L., L. A. Pogell and M. Kunnell. A two enzyme system for phosphorylation of nucleoside 5'- and triphosphates. Arch. Biochem. 1956, 65, 488.

Strominger, J. L., H. J. Koller, A. Axelrod, and E. S. Maxwell. Enzymatic oxidation of uridine diphosphate glucose to uridine diphosphate glucuronic acid. J. Am. Chem. Soc. Chem. 80, 1958.

Strominger, J. L., and O. Lowry. Quantitative histochemistry of [illegible] lactic, malic and glutamic dehydrogenases. J. Am. Chem. Soc. In press.

Kunnell, E. M., and J. L. Strominger. The reactivation of yeast inositol transaldolase. J. Gen. Physiol. 1958. 41, 761.

Kunnell, E. M., and J. L. Strominger. The effect of a component of yeast on the growth of streptomycin sensitive and resistant strains of [illegible] haemolyticus. Biochemistry. Vol. VI No. 4, 1959.

17. [illegible]

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pharmacology and Toxicology
LABORATORY

3. Pharmacology
SECTION

4. Bethesda
SECTION

5. [illegible]
[illegible]

6. Metabolic Processes, Ionic Action and Physical Chemistry Related to Membrane Distribution and Bioelectrical Phenomena as Exemplified by Nerve.
PROJECT TITLE

7. Dr. Abraham M. Shanes
PRINCIPAL INVESTIGATOR

8. Mr. Morris Berman
OTHER INVESTIGATOR

9. PROJECT DESCRIPTION:

Objectives: To determine the effect of metabolic inhibition and anesthesia of drugs which at concentrations actually occurring have a demonstrated effect on electrolyte distribution, and at concentrations the ionic action or the kinetics of many cellular processes and potentials in nerve. The relation of these to the metabolic cellular membrane potentials and to the production of action potentials also is to be established.

Method Employed: Unmyelinated splenic nerves of the land snail are studied in normal saline to particularly favorable preparations, and exposed in vitro to radioisotope solutions and the kinetics of entry and exit are followed under conditions of metabolic inhibition and the presence of anesthetics, drugs or modified saline. The magnitude of bioelectrical potentials under similar conditions can be followed with suitable electrical equipment.

Major Findings: Vertebrate nerve preparations have been found and methods of study have been developed which permit a discrimination of ions located in the extracellular spaces from those in the cells proper. They also permit the study of the rates of entry and exit of the ions through the fiber membrane under generally steady state conditions as well as under a variety of experimental conditions. Thus, it has been possible to show that the respiratory activity for the emergence of sodium and chloride from the fibers is to a great as that from the extracellular spaces. The escape of sodium is not markedly affected by oxygen lack even when combined with inhibition of glycolysis. However, return to oxygen following anoxia causes an acceleration of sodium efflux.

Single nerve fibers such as from the squid exhibit a [illegible] appears to be comparable to the extracellular space. In [illegible] preparations oxygen lack slowed sodium escape but accelerated potassium emergence. Cocaine slowed potassium efflux but not that of sodium.

Significance to NIMH Research: By the demonstration of the relation of metabolic processes and their derangement to normal functioning and malfunctioning of cells as exemplified by nerve (which in many respects is quite similar to other cells of the body), a basis is being laid for an understanding of the nature of [illegible] ces associated with metabolic diseases and for the development of means of treatment. The ease with which ions of connective tissue may be obtained by deshealthing nerves commends their use for study of burns, hormones, etc. on their permeability, structural, and [illegible] characteristics.

Proposed Course of Project: Sodium, chloride and potassium radioisotopes will be employed in studying the specificity (a) of metabolic inhibition-induced by oxygen lack, glycolysis inhibition (iodoacetate poisoning), azide and dinitrophenol — (b) of drug action, as exemplified by anaesthetic agents such as cocaine and excitatory agents like veratrine alkaloids and (c) of the basic milieu on the transfer of these ions out of and into the nerve fiber. Time and space permitting, exploratory studies will be attempted to correlate the biophysical phenomena of tissue nerves with their chemical findings.

Budget Data Sheet

10. 41430 - 8212A-71
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	ADJUSTED POSITIONS			MAN YEARS			OTHER USES
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	17,100	2	0	2	2	0	2	
FY 1956	17,100	2	0	2	2	0	2	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATIVE UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1955 OR 1956. IF COOPERATING UNIT IS OTHER THAN INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NAME IT:

None

14. IF THIS PROJECT RESULTED, DIRECTLY, OR INDIRECTLY, IN PUBLIC HEALTH RESEARCH IN THE PUBLIC HEALTH SERVICE (WITHOUT EXTRACTION OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (IF NONE, NO. 13 IS NEGATIVE, SAY)

None

Honors, Awards, and Public Service Since

15. NIMH - 6212A-71
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN [illegible] THAT THEY [illegible] DURING CALENDAR YEAR 1954:

Shanes, A.M. "Effects of sheath removal on the sciatic of the frog." J. Cell. Comp. Physiol. 43:37, 1954.

Shanes, A.M. "Effects of temperature on potassium liberation during nerve activity". Am. J. Physiol. 177:377, 1954

Shanes, A.M. "Sodium exchange through the epineurium of the bullfrog sciatic." J. Cell. Comp. Physiol. 43:99, 1954.

Shanes, A.M. "Factors governing ion transfer in nerve." Suppl. Physiol. Rev. In press.

17. LIST HONORS AND AWARDS TO WHICH CALLING IN THE FIELD OF [illegible] DURING CALENDAR YEAR 1954:

Dr. Shanes was selected as organizing chairman of the Symposium on "Electrolytes in Biological Systems", which was to have been held at Woods Hole, Mass. on August 4, 1954 by the Society of General Physiologists.

Dr. Shanes is to be editor of a monograph on "Electrolytes in Biological Systems" to be published by the Am. Physiological Society with the support of the National Science Foundation.

N.I.H.-A.

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pharmacology and Toxicology
LABORATORY

3. Pharmacology
SECTION

4. Bethesda
LOCATION

5. [illegible]
SERIAL NUMBER

6. The chemotherapy of mouse leprosy. Toxicology of isolates and related compounds
PROJECT TITLE

7. Y. T. Chang (fellow), W. F. von Oettingen, S.H. Webster, E.L. Jansen
PRINCIPAL INVESTIGATORS

8. Mary S. Rice
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The toxicology and evaluation of therapeutic effectiveness of drugs in leprosy. The toxicology of isolates as a basis for isolated salt to prevent goiter. The relation of iodine of compounds to physiological activity.

Major Findings: Methods have been devised for quantitative evaluation of drugs in leprosy, using intraperitoneally infected mice. Several compounds have been found superior to the sulfones, which at present are the basis of human therapy. The [illegible]mycin, Promizole, and certain sulfones represent the order of effectiveness. Combination therapy showed an additive but not synergistic effect. Experiments indicate that prolonged therapy may result in the acquisition of tolerance by the bacteria. Attempts are being made for this organism. (Chang).

The acute toxicity of the isolates causes nervous symptoms, hematological changes and under certain conditions [illegible] doses. Sublethal doses administered in the drinking water for several months have been essentially devoid of toxicity and indicate the safety of iodate for use in iodized salt. Studies on the use of organ weight - body weight ratio as an index of toxicity are being continued. (Webster)

A survey of the clinical toxicity of the antibiotics has been made to evaluate their hazards in clinical use. A look at the toxicity of the halogenated hydrocarbons has been submitted for publication. (von Oettingen)

Budget Data Sheet

10. NIAMD - 6712A-7A
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	DESIGNATED POSITIONS PROF	OTHER	TOTAL	M.Y. MAN-YEARS PROF	OTHER	TOTAL	PROGRAM CODE
FY 1955	38,600	2½	2	4½	2⅔	2	4⅔	
FY 1956	38,600	2⅔	2	4½	2⅔	2	4⅔	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1955 OR 1956: IF COOPERATIVE UNIT IS A FOREIGN AGENCY, SPECIFY COUNTRY:

Dr. Chang (American Leprosy Foundation Fellow)

14. IF THIS PROJECT RESULTS, OR IS EXPECTED TO RESULT, IN INVENTIONS, DISCOVERIES, OR TRAINING OF PERSONNEL OF SPECIAL VALUE TO THE PUBLIC HEALTH SERVICE (WITHOUT REGARD TO PATENTABILITY, ROYALTIES, OR FUNDS), IDENTIFY SUCH RESEARCH. (IF SERIAL NO.(S) IS GIVEN, YOU NEED NOT DESCRIBE.)

None

15. NIAID - 02126-72
SERIAL NUMBER

16. LIST PUBLICATIONS ORIGINATING DURING PRIOR FISCAL YEAR FROM PROJECT:
1954:

Sulfone therapy in mouse leprosy. Y.T. Chang, R.K. Wilson and [illegible]. Med. Clinics of North America, 1954; 38: 599.

Chemotherapy of Murine Leprosy. III. Comparative Activity of Diaminodiphenyl Sulfone and Pyrazinamide on Mouse Leprosy. Internat. J. of Leprosy. (In press)

IV. The effects of sulfisomezole, p-aminosalicylic acid, 2[illegible], 5 nitrofurans and 3 phenylthiourea compounds on mouse leprosy. Y. T. Chang. International J. of Leprosy. (In press)

17. LIST PUBLICATIONS AND WORKS TO BE PUBLISHED RELATED TO THIS PROJECT DURING YEAR 1954:

None

15. NIAID - RT12b-7s
SERIAL NUMBER

16. LIST PUBLICATIONS ISSUED DURING REVIEW YEAR. THIS SHOULD INCLUDE ONLY 1954:

Sulfone therapy in mouse leprosy. Y.T. Chang, R.H. Walcott and Ada Wedding. Med. Clinics of North America. 1954: 38, 599.

Chemotherapy of Murine Leprosy. III. Comparative Activity of Viomycin and Pyrazinamide on House Leprosy. Internat. J. of Leprosy. (In press)

IV. The effects of caithiazone, p-aminosalicylic acid, INH, 5 anti-acid 3 phenylthiourea compounds on mouse leprosy. Y. T. Chang. Internat. J. of Leprosy. (In press)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATED TO AREA PROJECT DURING REVIEW YEAR 1954:

None

15. NIAMD - 06124-7z
SERIAL NUMBER

16. LIST PUBLICATIONS (GIVE YEAR, AUTHORS, TITLE, JOURNAL, VOLUME, PAGE, AND YEAR) DURING THE PERIOD COVERED BY THIS REPORT (JULY 1, 1953 to JUNE 30, 1954):

Sulfone therapy in mouse leprosy. Y.T. Chang, R.H. Walcott and D.S. Wechsler. Med. Clinics of North America. 1954: 38, 599.

Chemotherapy of Murine Leprosy. III. Comparative Activity of Nicotinamide and Pyrazinamide on Mouse Leprosy. Internat. J. of Leprosy. (In press)

IV. The effects of antibiotics, p-aminosalicylic acid, 3211, 5 nitro-2-(3-phenylpropyl-amino) benzamide, 3 phenylthiourea compounds on mouse leprosy. Y. T. Chang. Internat. J. of Leprosy. (In press)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING THE YEAR 1954:

None

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pharmacology and Toxicology
LABORATORY

3. Pharmacology
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62(B)-12
SERIAL NUMBER

6. The physiological function, intermediary metabolism, and pharmacological [illegible] of spermine and related amines.
PROJECT TITLE

7. Drs. S.M. Rosenthal, Celia W. Tabor
PRINCIPAL INVESTIGATORS

8. E.C. Greene and E.L. Jackson
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: Spermine has been found to be a potent [illegible] agent. [illegible] it is widely distributed in mammalian tissues, its metabolism, function, and relation to general disease is being studied.

Methods Employed: An amine oxidase from beef plasma which degrades spermine and spermidine has been purified 200 fold. The products of degradation are being isolated and characterized, and their [illegible] determined. Attempts to find an antagonist to the spermine oxidase are being made, using mice as the test subject. Studies have been initiated upon mutant organisms and bacteria to find bacteria that require spermine, as a tool to elucidate the physiological [illegible]. Chromatographic methods for estimation of [illegible] have been developed.

Major Findings: Spermidine, putrescine and an amine aldehyde have been isolated from beef plasma and have been demonstrated as enzymatic breakdown products of spermine. Since ethylene and propylene diamine are ethylene amines also have similar nephrotoxic effects, attention is focused on an amine aldehyde or a cyclic derivative as the cause of kidney damage.

Administration of the enzyme will protect rats against [illegible] more lethal doses of spermine.

The oxidation products of spermine have marked toxic effects on bacteria and pure cells. Thus, several species of bacteria and spermatozoa are killed by low concentrations of spermine in the presence of the enzyme. This suggests a physiological significance and also affords an additional tool for elucidating mechanisms of action.

The distribution of spermine and spermidine in various tissues has been determined.

Project Description (Next Continued)

Significance to NIAMD Research: Spermine and spermidine are widely distributed in mammalian and plant tissues but no clear function has been demonstrated. Our physiological function or relation to disease. It is believed that this work will throw light on biochemical significance, and that a causative relationship is shown to some types of human renal disease.

Proposed Course of Project: (a) Further identification of the breakdown products of spermine and spermidine, and their relation to kidney damage.
(b) Further functional and pathological studies of the kidney after administration of spermine or its breakdown products.
(c) Measurement of spermine in blood and urine after experimentally produced renal lesions.
(d) Study of the lethal effects of the breakdown products on bacteria and spermatozoa to elucidate the mechanism and to obtain an antidote to spermine toxicity.
(e) To study the biochemical significance of these values by use of mutant bacteria and by isotopic labeling.
(f) An improved method of synthesis of spermine and spermidine is in progress, which will make these compounds more available and facilitate isotopic labeling.

10. NIAMD - 62124-73
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	PROFESSIONAL PERSONNEL			OTHER PERSONNEL			PROJECT DATES
		PHS	OTHER	TOTAL	PHS	OTHER	TOTAL	
FY 1955	36,200	2½	2	4½	2½	2	4½	
FY 1956	38,300	3	2	5	3	2	5	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

GRANTS & APPROVAL [ ] EXPANDED ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATIVE UNITS OR THAT DIRECTLY SERVE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL 1955 or 1956: IF COOPERATING UNIT IS NIH, GIVE INSTITUTE SERIAL NO.

Section of Pathologic Anatomy, LPH (NIAMD - 62162-51

14. IF THIS PROJECT RESULTED, OR IS EXPECTED TO RESULT, IN ANY INVENTIONS OR DISCOVERIES TO THE PUBLIC HEALTH SERVICE (WITHOUT LIBERATION OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH DISCOVERY: (GIVE SERIAL NO. (S) IF GIVEN NIH)

None

15. NIAMD - 6212b-73
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN [illegible] FOR THE PERIOD DURING [illegible]
1954:

"Pathology and Pathogenesis of Spermine Induced Renal Lesions." W. [illegible] and S. M. Rosenthal. Arch. Path. 1954; 57, 644.

"Purification of Amine Oxidase from Beef plasma". C. M. Tabor, [illegible] S.M. Rosenthal, J. Biol. Chem. 1954; 208, 645.

17. LIST HONORS AND AWARDS TO PERSONNEL [illegible] IN THIS [illegible] DURING [illegible]
YEAR 1954:

None

Honors, Awards and Publications Report

15. NIAMD - 6212h-73
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN REPRINTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"Pathology and Pathogenesis of Ethionine Induced Renal Disease." E. A. Zimmerman and S. M. Rosenthal. Arch. Path. 1954. 57, 244.

"Purification of Amine Oxidase from Beef Plasma". C. M. Kaburi, M. Kinsel and S.M. Rosenthal, J. Biol. Chem. 1954. 208, 845.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATED TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pharmacology and Toxicology
LABORATORY

3. Pharmacology
SECTION

4. Bethesda
LOCATION

5. NIAMD - 62124-74
SMITH NUMBER

6. Mechanisms and therapy of traumatic shock
PROJECT TITLE

7. Dr. R. Carl Millican and Dr. S. M. Rosenthal
PRINCIPAL INVESTIGATORS

8. Dr. Kehl Markley and Mr. E.F. Stohlman,
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: (1) Study the role of fluids, electrolytes and plasma proteins in the cause and treatment of shock. (2) Cause and therapy of late deaths in burn shock. (3) Clinical evaluation in burn shock of the effectiveness of large volumes of saline solutions.

Methods Employed: 1. Standardized traumatic shock produced in mice by application of tourniquets to hind legs or dipping animals in hot water. Mortality studies, analyses of fluid, electrolyte and colloid distribution employed to study mechanisms for effectiveness of fluid therapy in treatment of shock. Isotopically labeled plasma proteins and sodium used for distribution studies.
2. In the clinical study of burn shock plasma therapy is compared with large volumes of saline solutions on an alternate case basis. Clinical study (in cooperation with Research Grants Division of CIH) is in progress in Lima, Peru. Patient material consists of burn cases admitted to charity hospitals in Lima. The study includes serial measurements of hemodynamic effects of therapy; sodium, potassium and fluid balance studies; rate of gastrointestinal absorption; measurements of plasma volume after therapy.

Major Findings: 1. Demonstration of the therapeutic effectiveness of intraperitoneally administered whole blood, plasma, albumin in saline and saline in the treatment of burn shock in mice.
2. Radioactive tracer studies indicate that, as swelling occurs, protiens of the plasma rapidly exchanges with the plasma proteins accumulating in the injured area. After swelling is complete, the exchange of protein in the fluid accumulated in the injured area is greatly prolonged, indicating a sluggish pool.

3. Demonstrated in what plasma therapy be most effective administration is delayed until the initial swelling of tissues was complete. Saline therapy in equivalent volumes, whether started before or after swelling was complete, was not as effective as delayed plasma administration.

4. Preliminary evidence of the clinical efficiency of large volumes of saline in burn shock. With approximately 100 cases in each group, results to date indicate equal effectiveness of plasma therapy and saline therapy. No toxic effects from large volumes of saline therapy. No toxic effects from large volumes of saline were observed.

Significance to WRAIR Research: Knowledge of the fluid, electrolyte and cellular disturbances which occur in shock are of interest in the understanding of metabolic diseases.

Proposed Course of Project: 1. Future work will be concerned with further quantitative studies on the distribution of large electrolytes and proteins in the schocked animal and with evaluation of relative efficiency of fluids administered in shock and the factors affecting their therapeutic effectiveness. Work will be continued on the cause and therapy of late deaths following extensive burns in animals and in man.

2. The clinical study, of burns in Iran, Para has entered the evaluation phase of the project. For the next 12 months or so all burns will receive a comparison will be made of large volumes of saline solution with plasma supplemented with sufficient saline to make the fluid and electrolyte equivalent in both groups.

10. NAMRU - 6213A-7A
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	ALLOCATED POSITIONS			MAN YEARS			PROJECT CODE
		PMRC	OTHER	TOTAL	PMRC	OTHER	TOTAL	
FY 1955	45,700	3½	2	5½	3½	2	5½	
FY 1956	47,700	3½	2½	6	3½	2½	6	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] PUBLIC HEALTH ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL 1955 or 1956. IF COOPERATING UNIT IS WITHIN NIH ALSO GIVE SERIAL NO (S.)

Dr. Hurtado, Lima Peru Unit Study, Instituto de Biologia y Psicologia
Hospital Arzobispo - Loayza, Lima, Peru

14. IF THIS PROJECT ASSEMBLES, COMPILES, OR PARALLELS RESEARCH NOT CURRENTLY IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (1) SCHEDULE NO. (S) IF WITHIN NIH)

None

Honors, Awards, and Publications Sheet

15. NIMH - 6212-4-74
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN REPRINTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Rosenthal, S.M. and R. Carl Millican, "The role of fluids, electrolytes, and plasma proteins in experimental traumatic shock and hemorrhage". Physiol. Rev., December, 1954.

Millican, R. Carl, "S-35-Plasma and erythrocyte distribution in tourniquet-shocked mice". Am. J. Physiol., 179, December, 1954.

Millican, R. Carl, "Tourniquet shock in mice. Na^{22} and S^{35}-plasma volume of the accumulated fluid in the area of injury". Am. J. Physiology, 179, December, 1954.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

1. National Institute of Arthritis and Metabolic Diseases

2. Pharmacology & Toxicology Laboratory

3. Biochemical Pharmacology Section

4. Bethesda Location

5. NIAMD - 61LC-75 Public Health Service

6. Elucidation of the Enzymatic Mechanisms for the Biosynthesis of Adrenergic and Monoamine
Project Title

7. Simon Black
Principal Investigator

8. Mrs. Nancy G. Wright
Other Investigator

9. Project Description

Objectives: A major objective is the discovery of mechanisms of [illegible] acids for transformation into products.

Methods Employed: Cell-free enzyme extracts of plant and animal tissues and of bacteria are prepared and tested for their ability to catalyze the conversion of radioactive aromatic acid to adrenergic and monoamine. Standard tests for such conversions are employed.

Major Findings: It has been shown for the first time [illegible] that aromatic acid is a precursor of monoamine and adrenergic. The enzyme responsible for this conversion is widely distributed in plants. Extracts of spinach leaves possess a small capacity to form monoamine from aromatic acid.

Significance to NIAMD Research: Knowledge of the [illegible] enzymes [illegible] variety of amino acids in living cells will serve as a basis for greater understanding of the nature of disease and its more intelligent treatment.

Proposed Course of Project: The work will be pursued in the present manner until the individual chemical steps involved in the transformation of aromatic to monoamine and adrenergic have been established.

10. NIAID - 62125-75

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	AUTHORIZED POSITIONS: PERM	OTHER	TOTAL	AVG NUMBER: PERM	OTHER	TOTAL
FY 1955	19,000	1	1	2	1	1	2
FY 1956	19,000	1	1	2	1	1	2

12. BUDGET ACTIVITY:

RESEARCH - ☒ CONSULTATIVE ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL 1955 or 1956. IF COOPERATING UNIT IS NIH, USE NIH DIVISION SYMBOL (E)

None

14. IF THIS PROJECT ASSEMBLES, COMPILES, OR PACKAGES INFORMATION FOR DISSEMINATION IN THE PUBLIC HEALTH SERVICE (WITHOUT EXPENDITURE OF PROJECT FUNDS), IDENTIFY SUCH DISSEMINATION (BY SERIAL NO. (S) IF KNOWN)

None

35. [illegible]

16. [illegible]
1958)

Black, S. and Wright, N.G. Journal of Biological Chemistry (1955) 2. [illegible]

β-Aspartokinase and β-Aspartyl Enzymes

Aspartic β-Semialdehyde Dehydrogenase and Aspartic β-Semialdehyde

Homoserine Dehydrogenase

17. [illegible]
1958)

None

1. National Institutes of Arthritis and Metabolic Diseases
INSTITUTE

2. Pharmacology and Toxicology
LABORATORY

3. Biochemical Pharmacology
SECTION

4. Bethesda
LOCATION

5. PHAD - 62125-76
SERIAL NUMBER

6. Histidine, Histamine and Related Imidazoles
PROJECT TITLE

7. Herbert Tabor
PRINCIPAL INVESTIGATOR

8. A.H. Mehler, E. Adams, O.H. Barchiel, H. Bauer, (Fellow)

9. PROJECT DESCRIPTION

Objectives: To study the biosynthesis, interrelationships, and [illegible] of histidine, histamine and related imidazoles, and the biological activity of these compounds in order to understand [illegible] their physiological and pathological role.

Major Findings: The major findings during the past year have been the [illegible] that histidine decarboxylase acid ribotide is a major intermediate in the metabolism of histamine (Tabor, Hayaishi, Mehler). Further work has also been carried out on the nature of the [illegible] diary steps involved in histidine metabolism. (Tabor, Mehler) The immediate precursor involved in the [illegible] of histidine was synthesized, and identified as histidinal (Dr. Adams).

Significance to NIAMD research: Histidine is an essential amino acid, [illegible] into many important [illegible] metabolic relationships. The C-2 of the imidazole ring is important in [illegible] and is closely related to studies on the role of folic acid [illegible] lism. Changes in histidine metabolism have been described [illegible] alterations in the hormonal pattern, particularly in rheumatoid arthritis. Histamine is a powerful pharmacological agent which is normally present in tissues. It appears to be very important in gastric secretions, neurohormonal reaction to stress, certain types of [illegible] transmission, and in allergy and anaphylaxis. Histidine decarboxylase may be very important in stimulating the normal anterior pituitary [illegible] It is anticipated that further studies on the molecular interrelationship will aid in clarifying histamine's role in these phenomena.

Proposed Course of Project: I. Histamine Metabolism

A. Nature of other urinary metabolites after administration of histamine.

B. Enzymatic synthesis of 4-imidazolecarbonic acid riboside.

C. Enzymatic deformation of imidazolecarbonic acid.

D. Physiological and pharmacological studies as indicated by development of the project.

II. Histidine Metabolism

A. Purification of various enzymes involved in conversion of histidine to glutamic acid. Particular emphasis will be directed towards one-carbon transfer studies.

B. Biological synthesis and degradation of carnosine, anserine and other related imidazoles.

10. NIMH - 62125-76
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	DESIGNATED POSITIONS			MAN YEARS			CURRENT LEVEL
		PERM	OTHER	TOTAL	PERM	OTHER	TOTAL	
FY 1955	$1,800	3 1/3	2	5 1/3	3 1/3	2	5 1/3	
FY 1956	$7,700	4	4	8	4	3	7	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

SERVICE & APPLIED ☐ CONSTRUCTION ASSISTANCE ☐

13. IDENTIFY ANY COOPERATIVE UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL YEARS 1955 AND 1956. IF COOPERATIVE UNIT IS ALREADY WITH INSTITUTION SHOWN IN (1)

None

14. IF THIS PROJECT DUPLICATES, SUPPLEMENTS, OR PARALLELS RESEARCH BEING CONDUCTED ELSEWHERE IN THE PUBLIC HEALTH SERVICE OR OTHER FEDERAL OR PRIVATE AGENCIES, IDENTIFY SUCH DUPLICATION (BY SERIAL NO. (1) IF OTHER PHS PROJECT)

None

25. NIAID - 62125-76
Small mouse

26. LIST PUBLICATIONS ONLY THAT RESULTED FROM THIS GRANT/CONTRACT DURING CY 1954:

Preparation of Uroamic Acid. Eric Mehler, H. Tabor and D. Comar. Biochemical Prepns. In press.

Preparation of Histidinol. H. Tabor, C. Adams, and H. Tabor. Biochemical Prepns. Submitted.

Isolation of Formyl-L-Glutamic Acid from the enzymatic preparation of [illegible] H. Tabor, A.H. Mehler, J. Biol. Chem. Elected. 2, 1954.

Metabolic Studies on Histidine, Histamine and Related Substances. Herbert Tabor. Pharmacological Reviews, 6: 299-343, 1954.

Enzymatic Formation of Formylaspartic Acid from Dihydroorotic Acid. O. Hayaishi, H. Tabor and T. Hayaishi. J. Am. Chem. Soc., 76: 2279, 1954.

Synthesis of a Metabolic Product of Histidine. J.E. Sheppard, H. Tabor, A.H. Mehler, J. Am. Chem. Soc., 76: pp. 23, 6005, 1954.

27. LIST HONORS AND AWARDS RECEIVED BY PRINCIPAL INVESTIGATOR DURING CY 1954:

None

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Pharmacology and Toxicology
LABORATORY

3. Biochemical Pharmacology
SECTION

4. Bethesda
LOCATION

5. AM(D - 02125-07
GRANT NUMBER

6. Biosynthesis of Nicotinic Acid
PROJECT TITLE

7. Alan H. Mehler
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To isolate the individual steps in the sequence of reactions leading in nicotinic acid formation, to study the properties of the enzymes involved, and to characterize the intermediate metabolites.

Methods Employed: Enzymes are obtained from various sources and purified by the variety of modern extremely good in this field. Chemical and physical, especially spectrophotometric, methods are used to measure enzyme activity and to identify products. Possible substrates and products are synthesized by conventional organic chemical techniques.

Major Findings: The principal finding of the past year was the demonstration of a previously unknown enzyme from liver which effects the product of enzymatic oxidation of 3-hydroxyanthranilic acid. Earlier studies have indicated a sequence of reactions proceeding from tryptophan through kynurenine, kynurenic, 3-hydroxykynurenine and 3-hydroxyanthranilic acid to be involved in the biosynthesis of nicotinic acid. The two reactions using rabbit are the only known enzymatic reactions that continue this series, and therefore they must be studied to complete is an understanding of the mechanism of niacin synthesis.

Significance to NIAMD Research: The conversion of tryptophan to nicotinic acid is quantitatively important in man and laboratory animals. The present study is part of an attempt to elucidate the mechanisms involved in this transformation. Such information about this and other systems is necessary for an understanding of nutritional requirements and influences of diet and disease on nutritional requirements. At another level, it has already been shown

[illegible]

[illegible]

[illegible] tumorigenic effect on the level of the [illegible] oxidases tryptophan. The relation between this effect of [illegible] and its other biological effects is not yet clear, but there is [illegible] that more information at the enzyme level will help [illegible] mechanism of carcinoma acting.

Proposed Course of Project: Purification of the two enzymes concerned with 3-hydroxyanthranilic acid oxidation will be continued, and studies will be directed towards elucidation of the structures of the intermediate and final products. Attempts will be made to obtain cell-free systems to carry out the conversion of kynurenine to 3-hydroxykynurenine, and earlier steps in the biosynthesis of nicotinic acid.

Budget Data Sheet

10. AID/W - 62125-77
SERIAL NUMBER

11. PROJECT DATA:

	ESTIMATED EXPENDITURES	REQUIRED POSITIONS: TECH.	OTHER	TOTAL	U.S. DOLLARS: DIRECT	OTHER	TOTAL	OTHER DATA
FY 1955	6,900	2/3		2/3	2/3		2/3	
FY 1956	8,000	1		1	1		1	

12. MODES OF ACTIVITY:

RESEARCH	X	ADMINISTRATION	
REVIEW & APPROVAL		REGIONAL ASSISTANCE	

13. IDENTIFY BY COOPERATING UNITS OF THE UNITED NATIONS, ITS SPECIALIZED AGENCIES, PARTICIPATING NATIONS, PARTICIPATING FUNDS, & AGENCIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL YEAR 1955 or 1956. IF COOPERATING UNIT IS AID/W OR EMBASSY MARK AS (C)

None

14. IF THIS PROJECT RECEIVES, OR RECEIVED, OR PARTICIPATES, OR PARTICIPATED IN THE PUBLIC HEALTH SERVICE (INCLUDING EXPENDITURES OF COUNTERPART FUNDS), IDENTIFY SUCH PARTICIPATION: (BY CLASS NO. (3) OF ITEM (13)

None

Levey, Howard, and Publication Grant

15. NIAMD - AM21185-17
Serial Number

16. LIST PUBLICATIONS RESULTING FROM THIS PROJECT DURING THE CURRENT BUDGET PERIOD
1964:

Tryptophan Metabolism. Chapter in Symposium on Amino Acids, edited by W. D. McElroy and B. Glass. The Johns Hopkins Press, Baltimore (In press).

17. LIST HONORS AND AWARDS TO PROFESSIONAL PERSONNEL ON THIS PROJECT DURING THE
1964:

None

1. National Institutes of Health, Bethesda, Maryland
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Molecular Biophysics
SECTION

4. _____
LOCATION (IF OTHER THAN PREVIOUS)

5. NIAMD- Z01 AM-00126-08
SERIAL NO.

6. The personal chemistry of membranes and complex membrane systems: Biological interests.
PROJECT TITLE

7. Dr. Karl Sollner
PRINCIPAL INVESTIGATOR(S)

8. Dr. Ron Mallaf and Dr. Sheldon Dray, Drs. Goldfisch and Dr. Sweeney
OTHER INVESTIGATORS

9 PROJECT DESCRIPTION

Objectives: A physicochemical study of membranes and membrane model systems, with the purpose of providing a reliable physicochemical basis for the elucidation of numerous processes in living organisms, for instance, electrolyte balance and electrolyte distribution, the accumulation of electrolytes by living cells, cell and nerve potentials, and electrophysiology in general.

Methods employed: The preparation of membranes of highly controlled and specific electrochemical properties (the methods being developed mostly by the principal investigator and his collaborators) and the investigation of these membranes by physicochemical, electrochemical methods, such as potential and resistance measurements, also by chemical analytical procedures, including radioactive tracer methods.

Major Findings: A mechanism was suggested which explains the accumulation of electrolyte, both cations and anions, against concentration gradients. It involves two Donnan membrane equilibria that occur independently across a cation-permeable, anion-impermeable cation-selective membrane and an anion-permeable, cation-impermeable permselective membrane which separate an "inside" and an "outside" solution, the system being electrically a 1-compartment arrangement but a 2-compartment arrangement with respect to concentration. Experiments have shown a 30-fold accumulation of electrolyte. (Sollner.)

It was shown that the dynamic membrane potentials which arise in systems with inert and very reactive species of ions of the same sign of charge and with appropriate permselective membranes can be precalculated with a high degree of accuracy on the basis of previously developed concepts. (Lewy and Sollner,)

A theory was tentatively worked out which explains on a strictly physicochemical basis the differential accumulation of different species of ions of the same sign of charge across a permselective membrane, for instance, the preferential accumulation of potassium over sodium, or of iodide over chloride.

Significance: In order to understand electrolyte relationships in living cells and tissues, it is necessary to have accurate information on membrane model systems which, under carefully controlled known conditions, reproduce at least some of the major in vivo phenomena. The in vitro model of electrolyte accumulation constructed during the current year is the first instance in which a confining system accumulates both anions and cations simultaneously against concentration gradients, thus simulating one of the most basic and most common cell activities.

The study of polyionic potentials in synthetic membrane systems may put on a general rational basis which might be an enormous help in the clarification of many basic questions in electrophysiology such as resting and action potentials.

Proposed course of project: Completion of the work on bi- and polyionic potentials (Lewy and Sollner). Continuation of the work on the preparation of strong base type membranes (Gottlieb, Meinz and Sollner). Continuation of the studies on the kinetics of the rate of exchange of ions across membranes of high ionic selectivity and the correlation of these rates to other properties (resistance) of the membranes (Gottlieb and Sollner). A study of concentration cells involving the divalent alkaline earth cations and the recently developed strong acid type sulfonated polystyrene collodion membranes (Wagner & Sollner). Continuation of the experimental test of the above-indicated theory of differential absorption of ions of the same sign of charge.

10. GRANT NUMBER(S)
PROJECT NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN-YEARS			PAYABLE DATE
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	26,900	3		3	3		3	
FY 1956	26,900	3		3	3		3	

12. BUDGET ACTIVITY:

RESEARCH ☑ ADMINISTRATION ☐
ANALYSIS & EVALUATION ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ALL COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE INVOLVED, IN TERMS OF LOCATIONS, PERSONNEL FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN CURRENT FISCAL YEAR. IF NONE AVAILABLE ENTER 0. (GIVE NAME AND INDICATE SOCIAL SECURITY NUMBER)

Dr. Nelson Griffith, Laboratory of Biology and Biochemistry Section, National Naval Institute, is assigned to the University of the principal investigator and carries out under the latter's supervision the study on the evolution of cutaneous systems. He also participates in the preparation of written technical reports.

Dr. Israel Kapner of Vienna, Austria, assigned through the Institute of International Education to the principal investigator's laboratory.
(See sheet.)

14. IF THIS PROJECT DESCRIBES, COMPLEMENTS, OR PARALLELS RESEARCH BEING CARRIED ON IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY GRANT NO.(S) IF OTHER USE)

15. [illegible]
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Gregor, H. P. and Sollner, K., The potentiometric determination of cations and anions with permselective collodion and protamine-collodion membrane electrodes. J. Phys. Chem. 58, 409-415 (1954).

Sollner, K., with Sheldon Gray, Eugene Grim, and Max Nelhof, Electrochemical studies with model membranes, in "Ion Transport Across Membranes," edited by Clane T. Clarke, Academic Press, New York, 1954. pp. 144-163.

Nelhof, Max, The preparation and properties of arrow acid type collodion-base membranes. J. Phys. Chem. 58, 916-925 (1954).

Sollner, K., The electrochemistry of porous membranes, in "Electrochemistry in Biology and Medicine," edited by Theodore Shedlovsky, John Wiley & Sons, New York. In Press.

Sollner, K., Sheldon Gray, Eugene Grim, and Max Nelhof, Membranes of high electrochemical activity in studies of biological interest, in "Electrochemistry in Biology and Medicine," edited by Theodore Shedlovsky, John Wiley & Sons, New York. In press.

Sollner, K., A physicochemical cell model which simultaneously accumulates anions and cations against concentration gradients, Arch. Biochem. and Biophys. In press.

Sollner, K., Discussion of the paper, "Biophysical Effects of Ultrasonic Energy on Carcinoma and their Possible Significance," by Justus F. Lehmann, Julia F. Herrick, and Frank H. Krusen, delivered before the Thirty-second Annual Scientific and Clinical Session of the American Congress of Physical Medicine and Rehabilitation September 10, 1954, Washington, D.C. In press.

Nelhof, M. and Sollner, K., A quantitative electrochemical theory of the electrolyte permeability of mosaic membranes composed of selectively anion-permeable and selectively cation-permeable parts, and its experimental verification. II. A quantitative test of the theory in model systems which do not involve the use of auxiliary electrodes. J. Gen. Physiol. In press.

16. PUBLICATIONS - CONTINUED

For limited circulation only:

Dray, Sheldon, A quantitative theory of dynamic polyionic (essentially amino) membranes of ideal ionic selectivity in terms of transference numbers and its experimental test with permselective membranes, Ph.D. Thesis, University of Minnesota, 1954. 223 typewritten pages.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Molecular Biophysics
SECTION

4. _____
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD- 62126-72
SERIAL NO.

6. Investigation of the macromolecular organization of living matter.
PROJECT TITLE

7. Dr. R. W. G. Wyckoff
PRINCIPAL INVESTIGATOR(S)

8. Dr. Louis W. Lakow, and Mr. V. M. Kaplan
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To gain information about the macromolecules that are essential constituents of living matter - to see how they are arranged in the structures they form and to see how this arrangement is altered by infectious and degenerative diseases; to study certain of these macromolecules (such as viruses) to purified form after isolation from the living material.

Methods Employed: The electron microscopy of microorganisms, cells, and tissues in suspension or thinly sectioned; the physicochemical characterization of macromolecular components isolated from such material using electron microscopy, X-ray diffraction and classical established techniques; the development of new physical procedures to further such characterization.

Major Findings: The work carried out in Bethesda during the last year has been devoted mainly to the discovery and investigation of unexpectedly well-ordered macromolecular structures in certain bacteria. Thus, in connection with our studies of the bacteriophages of the colon bacillus, a strain of the latter has been found with a capsule made up of striated fibers, rather than the usual amorphous gel. We have also found, and are studying in greater detail, bacteria with cell walls made up in part of perfectly ordered spherical macromolecules and with flagella [illegible]

Form 6

Revised 1/71 Property of the Regents, University

Project Examination Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Chemical Biology
LABORATORY OR BRANCH

3. Molecular Biophysics
SECTION

4. _____
LOCATION (IF OTHER THAN BETHESDA)

5. CHAMP- 68186-13
SCHEDULE NO.

6. Investigation of the macromolecular organization of Avian myeloblastosis virus

7. Dr. J. M. D. Olmsted
PRINCIPAL INVESTIGATOR(S)

8. Dr. Lodge de Jesus, and Mr. J. A. Hodge
OTHER INVESTIGATORS

9. Project description:

Objectives: To gain information which will be commensurable with any conclusions or findings which may be arrived at by the investigators in the electrical field and to use the information to advance the knowledge of the structure and organization of viruses in relationship with biochemical studies. To study certain of these macromolecules (such as viruses) in purified form (isolated from the living material).

Methods Employed: The electron microscopy of macromolecules, cells, and tissues in suspension or single sectioned; the preparation, concentration of macromolecular components isolated from the material using standard techniques; X-ray diffraction and scattering techniques; the development of new improved techniques in electron microscopy.

Major Findings: The work carried out in Bethesda during the last year or two has served mainly to the discovery and investigation of particularly well-ordered macromolecular structures in certain bacteria. Thus, in connection with our studies of the reproductive stages of the avian bacillus, a strain of the latter has been found with a capsule made up of crystalline sheets, perhaps four to seven molecules thick. In some other strains, not yet studied in greater detail, bacteria with well while cells do not appear to be perfectly crystal spherical macromolecules and viral filaments that

9. PROJECT DESCRIPTION - CONTINUED

are helical structures showing an underlying regularity in macromolecular composition.

During the last two years one of the principal investigators (Ralph W. G. Wyckoff) has been serving as Science Attaché at the U. S. Embassy in London. While there he has worked, partly as consultant to the NIH, and in collaboration with confreres at University College, London, and the Pasteur Institute, Paris, to develop methods for examining at electron microscopic magnifications tissues of the central nervous system before and after infection with neurotropic viruses. These investigations, which are to be continued here, have thus far shown new facts important to an understanding of the structure of healthy nerve tissue and of the growth of rabies and poliomyelitis in this tissue.

Significance to NIAMD Research: Planned as a program of fundamental research, most of our results will only later be applicable to the specific pathological conditions, such as arthritis, with which this Institute is concerned. The studies we have made of the macromolecular texture of collagen [illegible] however, already providing fundamental background for interpreting pathological changes in connective tissue.

Proposed course of project: Besides the foregoing, emphasis for the immediate future is to be laid on (1) the further development of methods of electron microscopy to reveal increasingly small detail in biological structures, (2) the development of X-ray microscopy as a way of getting new information about the interrelations of structures of macromolecular dimensions and (3) the exploration of certain new physical microprocedures which may give new chemical information about these structures.

10. NIAMD- DCLSB-12
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED OBLIGATIONS	BUDGETED POSITIONS: GRADE	OTHER	TOTAL	MAN YEARS: GRADE	OTHER	TOTAL	FUNDING SOURCE
FY 1955	$3,400	3	3	6	3	3	6	
FY 1956	$3,400	3	3	6	3	3	6	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL YEAR 1955 OR 1956. IF COOPERATING UNIT IS WITHIN NIH GIVE ITS SERIAL NO.(S) IF KNOWN

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH BEING CONDUCTED IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

N.I.H. — [illegible]
November 1954 [illegible]

Honors, Awards, and Publications Data

15. NIAMD- 02105-07
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Lehar, L. M. and Mosley, V. M.: Demonstration of striated fibers in the capsule of the Lisbonne strain of Lysogenic Escherichia coli. J. Bact., 67: 576-578, May 1954.

Lehar, L. M. and Mosley, V. M.: Periodic structure in the flagella and cell walls of a bacterium. Biochim. et Biophys. Acta, 13: 325-331, Nov. 1954.

Nora, Haruhiko: The dimensions of T series bacteriophages of Escherichia coli B. Biochim. et Biophys. Acta, 12: 495-499, Dec. 1953.

Wyckoff, Ralph W. G.: Electron microscopic evidence on virus proliferation. (Symposium on the Interaction of viruses and cells.) 8th International Congress of Microbiology, Rome, Italy. September 7-14, 1953.

Wyckoff, Ralph W. G.: The Electron Microscope in Biology. The Isaac Newton Lecture of The Royal Institution of Great Britain. Nature, 173: 419, 1954.

Wyckoff, Ralph W. G.: Some thoughts on the future of natural science, with illustrations from the growth of X-ray diffraction work in the United States. Brit. J. Appl. Physics, 5: 299-304, 1954.

Wyckoff, Ralph W. G.: Introduction to Symposium on Submicroscopic Organization of Cytoplasm. (Leiden, The Netherlands - September 1-8, 1954.) To appear in Proc. of the VIIIth Congress of Cell Biology.

Young, J. Z. and Wyckoff, Ralph W. G.: The Nodocneuron Surface. (In press)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Ralph W. G. Wyckoff - President, International Union of Crystallography
Ralph W. G. Wyckoff - President, Joint Commission (of IGSU) on Electron Microscopy.

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology 3. Photobiology
LABORATORY OR BRANCH SECTION

4. _____ 5. NIAMD- A01127-03
DIVISION (IF OTHER THAN BETHESDA) SERIAL NO.

6. Ionization studies in the upper atmosphere.
PROJECT TITLE

7. Dr. Jerman Jacobs
PRINCIPAL INVESTIGATOR(S)

8. Maynard M. Smith, Jr.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The study of the characteristics of fundamental particles created in the interaction of high energy ($\geq$ 2 Bev) cosmic ray particles with air nuclei. This is primarily of importance to our understanding of nuclear forces and weak physics. The subject is also of biological significance in the interpretation of the radiation hazards associated with high altitude (40,000 ft. and up) manned vehicles.

Methods Employed: Exposure of nuclear emulsions in rockets and high altitude balloons (Skyhooks).

Major Findings: Of current theoretical interest is the formation of nuclei with one of the neutrons substituted by a lambda-particle. We have made an important finding in showing the mesonic decay of an emitted proton from which it was possible to deduce the binding energy of the lambda-particle in this strange nucleus.

Our observation of the crossing of a relativistic carbon nucleus through tissue has proven of interest to the U. S. Air Force (see report by Major David G. Simons, U.S.A.F.(MC) published in the J. Aviation Med. 25, 380 (1954)).

7. [illegible] (Continued)

Significance to Military Research: Basic research which may have significance of military or health importance.

Proposed Course of Project: In an effort to establish the number of [illegible] primary hits passing through maximum [illegible] tion in tissue, a phantom of a human head is to be flown by the U. S. Air Force in the spring of 1955. This will contain emulsion detectors for establishing the number of "thin-down hits" (believed to be the greatest radiation hazard from cosmic radiation) in the brain and the eyes.

Budget Data Sheet

10. NIAID- 62131-00
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	FACILITIES AND SERVICES DAYS
FY 1955	14,700	1	1	2	1	1	2	
FY 1956	14,700	1	1	2	1	1	2	

12. RESEARCH ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

PATIENT & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY CONTRACTING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL YEAR 1955 or 1956. IF COOPERATING UNIT IS WITHIN THE DEPARTMENT SERIAL NO.(S) (FY56)

Cooperating Units: 1. Naval Research Laboratory Rocket Panels.
2. Office of Naval Research Bellows Project.
3. U. S. Air Force.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH. (BY SERIAL NO.(S) IF WITHIN NIH)

15. AT(40-1)-2017-23
DALLAS 9C.

16. LIST PUBLICATIONS ISSUED FROM RESEARCH FROM THIS PROJECT DURING CALENDAR YEAR 1954:

A. Yagoda. Occurrence of a fission-dust particle in a nuclear emulsion. Nature 173, 77 (1954). Also New York Times, Jan. 9, 1954, page 1.

H. Yagoda and Howard S. Smith, Jr. Observations on the penetration of heavy primary cosmic rays. J. Aviation Med. 25, 56-67 (1954).

H. Yagoda. Memorial of Olin T. Lee, Amer. Mineralogist 39, 677-679 (1954).

H. Yagoda, Isothermal processing of latent nuclear emulsions, Rev. Scientific Instr. In press.

H. Yagoda, Tracks of nuclear particles, Scientific American. In press.

H. Yagoda, Fine-grain production in a nuclear emulsion, Physical Review. In press.

H. Yagoda, Reconstitution of an aborted fission, Physical Rev. In press.

17. LIST AWARDS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Photobiology
SECTION

4. _____
LOCATION (IF OTHER THAN BETHESDA)

5. ZIAAM- 00127-07
SERIAL NO.

6. Investigations of the action of radiant energy on biologically important compounds, with emphasis on steroids.
PROJECT TITLE

7. Mr. Norman E. Sharpless and Dr. F. S. Brackett
PRINCIPAL INVESTIGATOR(S)

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objectives of this project are the establishment of the structures of the various products and intermediates of the steroids and the fixation and quantum efficiencies of their activation by radiant energy.

Also during the past year a series of studies was completed on the high energy radiation of aqueous solutions of amino acids.

Methods employed: Methods utilized consist of the ultraviolet irradiation, analysis, and isolation of the products, using physicochemical and physical techniques including ultraviolet and infrared spectroscopy, X-ray diffraction and optical rotations.

Major Findings: The preparation and isolation of vitamin D intermediates on a macro scale by the irradiation of ergosterol is a function of the physical set-up of the radiation and circulation equipment. The ratio between thickness of absorbing layer and the speed of circulation must be nicely balanced to give maximum yields of the desired products.

Commercial ergosterol has a tendency to turn yellowish on storage, especially in the air and light. Preliminary investigation of the

9. PROJECT DESCRIPTION -- CONTINUED

nature of the products formed seems to indicate that it consists of a retropeptic component of some type.

In the just completed study on the effects of high energy radiation on aqueous amino acids, there was found a general tendency for such radiation to react with the various acids to give analogous products. In general there is deamination to give the corresponding keto acids and beta acids, decarboxylation plus deaminization to give the aldehyde and decarboxylation to give the amine. In the cases of glycine and alanine these reactions occur with the same frequencies.

Significance to NIAID Research: A knowledge of the fundamental properties of the various biologically active materials is absolutely necessary for the complete understanding of their action in the cell, and is required for the discovery of fundamental or similar acting substances.

Proposed Course of Project: An intensive investigation of the infrared spectra of compounds related to those showing chemical or biological activity, in an attempt to correlate structural and chemical features with biological activity.

An instrument is being developed which will record the infrared spectrum in the region of 3 μ at high resolution. This is expected to yield information on hydrogen bonding of significance in this study.

10. NIAMD- 6012-C3
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	PROFESSIONAL POSITIONS PROF.	OTHER	TOTAL	MAN YEARS PROF.	OTHER	TOTAL	PERSONNEL TYPE
FY 1955	20,300	0½	1½	4	1½	1½	3	
FY 1956	23,300	2½	1½	4	2½	1½	3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN SECTION 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE BRANCH (DIVISION)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT DUPLICATION OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

Analysis of NIH Progress Statement

Honors, Awards, and Publications Sheet

15. NIAMD- 62127-01
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Swirbely, W. J. and W. E. Sharplese, The annealing of the thermoscope in the acetin lam, J. Am. Chem. Soc. 76, 1404 (1954). [From the Ph.D. Thesis of W. E. Sharplese--published through the University of Maryland.]

Maxwell, C. E., D. C. Peterson and W. E. Sharplese, The effect of isotonic radiation on amino acids. I. The effect of X-rays on aqueous solutions of cystine, Rad. Research 1, 530 (1954).

Sharplese, W. E., A. E. Blair and C. E. Maxwell, The effect of isotonic radiation on amino acids. II. The effect of X-rays on aqueous solutions of cystine. Accepted for publication in Rad. Research.

17. LIST NAMES OF AWARDS TO PERSONNEL CONNECTED TO THIS PROJECT DURING CALENDAR YEAR 1954:

None.

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Photobiology
SECTION

4. _____
LOCATION (IF OTHER THAN BETHESDA)

5. PHMP- 62127-03
SERIAL NO.

6. Effects of radiant energy on the oxidative metabolism and chemosynthesis in living cells
PROJECT TITLE

7. Dr. E. A. Olson and Dr. J. S. Brachet
PRINCIPAL INVESTIGATOR(S)

8. B. Chickard
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To study the specific effects of radiant energy on cellular oxidative metabolism and chemosynthesis utilizing the ultraviolet, visible, and infrared regions of the spectrum. To determine the role and identity of enzymes, photosensitizers, and pigments in the photochemical and other reactions involved. In addition, to identify the intracellular morphological changes associated with such metabolic effects in order to localize reaction sites and participating cell structures or inclusions.

Methods Employed: Cell suspensions of unicellular organisms (Chlorella,) cultured aseptically under various atmospherical conditions are irradiated in monochromator systems designed to permit homogeneous radiation of all cells. Special features are also provided to overcome the prevailing difficulties in the measurement of the energy absorbed by cells introduced through the nondirective scattering of light by such suspensions. Similarly the selective absorption and identity of pigments and other components is determined accurately in living cells. Simultaneous electrochemical

measurements of oxygen metabolism during prescribed radiation and dark intervals under various conditions of intensity, wavelength, added substrate, specific enzyme inhibitors, and pigment density provide quantum and kinetic data leading to the identity and nature of the photochemical and dark reactions involved. High resolution monochromatic photomicrography provides morphological data.

Major Findings: Methods developed for culturing cells under conditions which may control pigment density without limiting other aspects of normal growth and metabolism have established the dependence of quantum efficiency upon both pigment density and the relative proportion of pigment components.

Morphological effects such as cell size, pigment distribution and localization of storage products in the cell have been likewise associated with conditions governing pigment density and quantum efficiency.

Additional developments include: (1) a method for rapid automatic recording simultaneously of the rate of oxygen evolution of cell suspensions and the oxygen concentration (2) an integrating spectral differential recording spectrophotometer for use with living cell suspensions; (3) the adaptation of high intensity radiation sources for D.C. operation to provide steady and unmodulated monochromatic radiation at desired wavelengths; and (4) the utilization of the high speed micro-ball mill technique to obtain efficient disruption of mechanically resistant cells for complete extraction or separation of cell components.

Significance to NIAMD Research: Unicellular organisms with special metabolic adaptation for the utilization of radiant energy in chemosynthesis carry out to a marked degree but by different pathways the same general metabolic reactions which occur in the more specialized cells of higher organisms. During the synthesis of proteins, fats, oils, steroids and other cell components some mechanism for CO_2 assimilation is now considered to be operable in the normal metabolism of all cells. In cells not adapted to utilize radiant energy the energy source for this process is provided chemically via phosphate or other energy transferring systems. Radiant energy thereby becomes a tool in photosynthetic organisms by which specific metabolic pathways may be induced at will without changing in any other way the physical or chemical environment of the cell. Use of the appropriate wavelength and intensity of radiation may provide considerable choice in the degree of participation by known pigments in both synthesis and

9. PROJECT DESCRIPTION - CONTINUED

oxidative reactions while the duration and intensity of light allows for a kinetic study of the carboxylation-decarboxylation equilibrium. Information in this direction leads to a better understanding of the more subtle metabolic pathways which characterize anomalies in physiologically diseased cells.

Proposed Course of Project: Completion of the work involving quantum efficiency dependence upon quantitative and qualitative pigment development. Further emphasis on specific inhibitor and substrate effects and wavelength dependency of oxidative metabolism via pigment participation. Improvement of present electrochemical oxygen detection method and extension to include CO_2 measurement in cell suspensions.

Continuation of time course and kinetic studies of photo-inactivation lag under various conditions conducive to identity of the responsible process. Continuation of cytological studies with enhancement by appropriate histochemical techniques.

10. NIAMD-60227-02
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PROJECT DATE
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	36,600	2½	3½	6	2½	3½	6	
FY 1956	36,600	2½	3½	6	2½	3½	6	

12. GRANT ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. SUBMIT A JOINT COOPERATIVE PLAN OF THE PUBLIC HEALTH AGENCIES, OR CLINICAL ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL YEAR 1955 or 1956. IF APPROPRIATED UNIT IS ALREADY HAS INDICATE SERIAL NO(S) FROM [illegible]

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH NOW SUPPORTED BY THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF KNOWN)

None

15. NIAMD- 62127-02
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Olson, E. A. Physiological action of auxin, Physiol. Reviews (Accepted for publication).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

N.I.H.
Z-1

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Radiation Safety
SECTION

4. LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD- 62 M 26-03
SERIAL NO.

6. Radiation safety; metabolism of radioactive materials
PROJECT TITLE

7. Victor E. Archer
PRINCIPAL INVESTIGATOR(S)

Walter C. Weal
Joseph K. Brown

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To provide service and supervision which will promote the safe use of radiation at the NIH; to develop improved methods of decontamination, effective localization and waste disposal; to determine the metabolism, retention and excretion of certain radioactive materials and how this is affected by various factors such as isotope dilution and biological half-lifetime.

Methods Employed: Surveys of radiation producing machines and laboratories where radioactive materials are used; receiving, shipping, calibrating and delivering isotope shipments; collecting radioactive waste; doing physical counts and blood counts; animal studies on decontamination and waste disposal; the metabolism studies are done primarily with experimental animals, but may be done on individuals who have had an accidental intake of radioactive materials.

Major Findings: The exponential decrease with time of the excretion of beta by humans was further delineated; tuberculous animals were found to metabolize radiocobalt differently than normals; injection of to animals of a stable isotope of an element was found in some cases to affect the metabolism of its radioactive isotope even though the element was not a trace element; the concentration of radiostrontium within infarcted myocardium nearly as rapidly as it enters normal myocardium.

9. PROJECT DESCRIPTION - CONTINUED

Significance to IAEA Research: All knowledge of the metabolism of radioactive substances is applicable to a greater or lesser extent to normal metabolism which must be understood to study metabolic diseases; a possible development is a new method of therapy for accidental intake of radioactive substances.

Proposed course of the project: Continue the radiation safety service to the peak; continue the search as to the cause of the difference in metabolism of radioiodine in tuberculous and normal animals; expand the study of "isotopic flooding" to other elements; continue the work on decontamination of [illegible]

9. PROJECT DESCRIPTION - CONTINUED

Significance to NIAMD Research: All knowledge of the metabolism of radioactive substances is applicable to a greater or lesser extent to normal metabolism which must be understood to study metabolic diseases; a possible development is a new method of therapy for accidental intake of radioactive substances.

Proposed course of the project: Continue the radiation safety service as in the past; continue the research as to the cause of the difference in metabolism of radioiodine in tuberculous and normal animals; expand the study of "isotopic flooding" to other elements; continue the work on decontamination of electrolytic

N.I.H. - 7
December 1965

Budget Data Sheet

10. NIAMD- 62123-63
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	GRADE AVG
FY 1966	24,300	1	3	4	1	3	4	
FY 1967	24,300	1	3	4	1	3	4	

12. BUDGET ACTIVITY:

RESEARCH ☑ ADMINISTRATION ☐

PROVISION & APPROVAL ☑ TRAINING (GRANTS) ☐

13. IDENTIFY THE COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OTHER FEDERAL AGENCIES, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL 1966 or 1966. IF COORDINATED DATA IS NEEDED SEE EXPLANATORY DETAILS (7-13).

Section on Hypoxic and Ischemic Diseases, NMI, under Dr. [illegible] will contribute personnel and facilities with regard to the studies on [illegible] ventricle. Serial number 71182.

14. IF THIS PROJECT RESULTS, CONTEMPLATED, IN PARALLEL RESEARCH BY OTHERS IN THE PUBLIC HEALTH SERVICE (AVOIDING DUPLICATION OF EFFORT), PLEASE IDENTIFY SUCH RESEARCH. (BY SERIAL NO.(S)) IF "NONE" YES

None

16. PHS-NIH- 62235-02
GRANT NO.:

18. LIST PUBLICATIONS WITHIN PAST TWO YEARS OR IN PRESS OR ACCEPTED FOR PUBLICATION
1964:

Lemmon, W. D. and T. E. Newhall, Radiation sensitization with [illegible]
Study. Accepted by Am. J. Roentg. Rad. Therap.

17. LIST HONORS AND AWARDS OF SCHOLARLY ACTIVITY FOR PERIOD INDICATED
(YEAR 1964):

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR DIVISION

3. Physiology
BRANCH

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NIAMD- 66(2)-C
STAFF NO.

6. Pulmonary ventilation
PR. TITLE

7. Diving Sports
PHYSICAL INVESTIGATION(S)

8. Julius F. Brahinsky
Alfred B. Gaffe
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The studies in pulmonary ventilation at this laboratory concentrated from observations made in low and normal density atmospheres. Studies in high density atmospheres are now in progress as embodied in a subproject on the physiology of underwater swimmers.

Objectives: The principal objective of the over-all project is to evaluate phenomena regarding breathing, heretofore with regard to their physiological significance. In order to accomplish this objective studies of physiology must be undertaken in order to accurately control the experimental situation. Thus, in underwater problems it is hoped that ultimately breath velocity patterns at various depths may yield information that can be compared with our findings at high altitude. An interim objective the physiology of closed underwater swimmers is being studied on contract to the Office of Naval Research. This is the third year of this support.

Methods Employed: Subjects are studied for oxygen consumption, CO2 production, breath velocity patterns, and other responses as necessary while swimming or resting immersed under controlled conditions of temperature, water speed, drag, etc. Since positive under water are less amenable to volumetric gas measurement than

the classical metabolic studies in air it has been necessary to devise special equipment for the various measurements. In addition, swimming facilities had to be set up for use in the laboratory as an alternate to the use of the circulating water channel of the David Taylor Model Basin which was placed at our disposal for limited periods in the past.

Major findings: The average efficiency of underwater swimming in this series did not exceed 5.1%. This was calculated on the basis of the difference between oxygen consumption during the drag measurements when swimmer activity was at a minimum and the oxygen consumption at known pace rates, compared with the actual work accomplished as determined by the drag data. At the highest pace rate (1.0 knot) the average work accomplished was about 900 ft. lbs./min. This corresponds to light work in air. The measurements of oxygen consumption, respiratory minute volume and breathing velocity, however, fell well within the known ranges for heavy work in air.

For long distance swimming a rate of 0.7 knots seems to be optimum under the conditions of this series of tests. At this rate swimming efficiency was maximum (5.1%) as was the coefficient of oxygen utilization (68 cc/liter of ventilation) and the calculated oxygen consumption per mile was lowest (approximately 70 L.).

Significance to NSMRL Research: In order to extend the understanding of both normal and abnormal respiratory gas exchange it has become necessary to explore the significance of phenomena beyond those used classically for measuring respiratory function. Inasmuch as physical environmental effects such as pressure, the study of atmospheric density effects on breathing will necessitate form a new set of criteria for judging the level of normal or abnormal behavior.

Proposed course of project: The contract with NSMRL is underway and will continue for 2 years. It is hoped that by that time basic information on breathing patterns will be in hand. It is planned that studies with artificially mixed atmospheres of various density to simulate the effect of depth can be set up for further research. A beginning has been made with swifter human subjects, but certain technical and toxicological difficulties must first be overcome.

[illegible]

10. [illegible]

11. [illegible]:

	Estimated Expenditure	Budgetary Requirements			Man Years			Supplementary Data
		Field	Others	Total	Field	Others	Total	
FY 1988	34,100	2	4	6	2	3	5	
FY 1989	34,100	2	4	6	2	3	5	

12. [illegible]:

Research ☒ Advisory ☐

Service & Advisory ☐ Combined Research ☐

13. [illegible]

(This project is being carried jointly by [illegible] during 1988 and 1989.

14. [illegible]

None

A.E.C. - 2
December 1954

Analysis of AEC Program Activities

Honors, Awards, and Publications Sheet

25. NIAMD. 62129-84
SERIAL NO.

26. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

There are no publications from this project. Reports have been sent directly to OWR on progress of the contract.

Black, Simon. Enzymatic reduction of β-aspartyl phosphate to homoserine. J. Am. Chem. Soc., 76: 5768, 1954. (Not reported in 1953 Annual Report.)

Smith, W. W., L. Genshory, I. Alderman and J. Cornfield. Effect of granulocyte count and litter on survival of irradiated mice. Am. J. Physiol., 178: (3) 474-476, Sept., 1954.

Smith, W. W., L. Q. Marston and J. Cornfield. Granulocyte count, resistance to experimental infection and spleen homogenate treatment in irradiated mice. Am. J. Physiol., 178: (2) 288-292, Aug., 1954.

Smith, W. W., W. Anderson and G. Ashwell. Spleen adenosine triphosphatase activity in irradiated mice treated with spleen homogenate. Am. J. Physiol., 178: (3) 471-473, Sept., 1954.

Smith, F., W. E. Smith, L. Genshory and W. H. Grenan. Effect of irradiation on resistance to infection in irradiated mice and rats. Proc. Soc. Exptl. Biol. Med., 87: (1) 23-26, Oct., 1954.

27. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Physiology
SECTION

4. _____
LOCATION (IF OTHER THAN BETHESDA)

5. PHS- 6214B-05
SERIAL NO.

6. Physics of gas diffusion into and through tissues
PROJECT TITLE

7. John S. Buck
PRINCIPAL INVESTIGATOR(S)

8. Margaret L. Kelaher
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: Our objective is to learn as much as possible about the factors which govern the passage of respiratory gases through biological structures, particularly in the gas phase and in the region of pure exchange, where gases enter and leave tissues. This involves the study of tissue permeability, mechanism of diffusion and respiratory responses to various gas concentration problems.

Methods Employed: We have used insect material because it is capable of much more drastic experimental alteration than that of any other air-breathing animal, and yet resembles lung-breathing vertebrates in having a direct tissue-gas exchange. Furthermore, in many instances respiration has been simplified to pure diffusive transfer, which is thus susceptible to precise analysis.

Major Findings: Analysis of two problems was completed during the past year. The first involved the mechanism of gas passage through the minute respiratory valves, the problem being raised by the fact that ordinary diffusion was calculated to account for only 10% of the observed oxygen uptake. Analysis showed that an unusual process, "pore-diffusion", hitherto known only in the green leaf, is responsible for the paradoxically high rates of gas passage. The second problem concerned certain insects which, at basal metabolic levels, expend from 60 to 1/4% of their respiratory CO_2 for long periods, during which O_2 uptake is steady and normal, then release the impounded CO_2 in

9. PROJECT DESCRIPTION - CONTINUED

in great gushes. The CO_2 retention was found to involve both mechanical damming by the air valves and CO_2 stabilization by tissue buffers, and to be primarily the result of provisions for water conservation.

Significance to NIAMD Research: Aside from their contribution to understanding of the little-known field of gas-liquid phase exchange in respiration, our studies have impinged directly on three aspects of human respiratory physiology. (a) The "pore-diffusion" analysis was useful in evaluating and suggesting methods of investigating the possibility (recently suggested by McClendon) that pore diffusion occurs through the alveolar necks of the lung; (b) the "CO_2 gush" analysis shed light on the analogous gas exchange which takes place in the human lung during breath-holding. (c) Some cooperative work we undertook with Dr. Jacob Verduin of Ohio State University stimulated him to make some new estimates of pulmonary gas transfer which cast doubt on accepted estimates of gas passage across the alveolar membrane.

Proposed course of project: Future projects planned include (a) tissue pO_2 distribution in hypoxia, and (b) physiological mechanisms of water retention.

N.I.H. - B
December 1984 Analysis of ADP Program Activities

Budget Data Sheet

20. NIAMD: 82129-85
SERIAL NO.

21. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1985	17,000	1	1	2	1	1	2	
FY 1986	17,000	1	1	2	1	1	2	

22. BUDGET ACTIVITY:

RENEWAL [X] ADMINISTRATIVE [ ]

REVISED [ ] TECHNICAL ADVANCE [ ]

23. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1985 or 1986. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (

None.

24. IF THIS PROJECT REQUIRES, SUPPORTING, OR PARALLELS RESEARCH NOW CONDUCTED IN THE PUBLIC HEALTH SERVICE (WITHOUT EXPENDITURE OF ADDITIONAL FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

Analysis of CNS Pathogen Activities

Honors, Awards, and Publications Sheet

15. NIAMD- A2120-BS.
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS WHICH THIS PROJECT DURING CALENDAR YEAR 1954:

Buck, J. B. Bioluminescence. In press in a symposial volume of the A.I.B.S.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954.

None

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Physiology
SECTION

4. _____
LOCATION (IF OTHER THAN BETHESDA)

5. PHMD- 6228-06
SERIAL NO.

6. The effect of synthetic plasma expanders on renal hemodynamics in dogs
PROJECT TITLE

7. Louise E. Marshall
PRINCIPAL INVESTIGATOR(S)

8. Charles W. Deane
OTHER INVESTIGATOR(S)

9. PROJECT DESCRIPTION

Objectives: Two principal objectives are served by a study of the effect of simultaneous administration of the synthetic plasma expanders, dextran and polyvinyl pyrrolidone (PVP). The first is to determine the capacity of the healthy dog's kidney to continue normal function under stress. This condition occurs during glomerular filtration of large amounts of the smaller molecular sizes of the injected colloid. Excretion of a second colloid at this time may alter renal function.

The second objective concerns the possibility that with 2 available plasma expanders available in time of emergency they might be used in the same person. Nothing is known of their compatibility.

Methods Employed: Renal clearances are determined of test substances which are accepted as measures in the dog of glomerular filtration, effective renal plasma flow, and tubular capacity for secretion and reabsorption. After a colony of dogs having normal values is established, they will be subjected to massive rapid injections of PVP, followed by dextran. When excretion of these colloids is at a maximum, renal function will be retested. Blood pressure will be followed to make sure that it remains within normal limits. Blood and urine concentrations of the expanders in addition to the clearance substances will be determined. Fractionation should also be measured, which necessitates renal vein catheterization. If facilities permit, the question of colloid storage should be studied by means of tissue analysis and histological sectioning.

3. PROJECT DESCRIPTION - NARRATIVE:

Major Findings: Several details of experimental procedures have been clarified this year, and are the subjects of 4 publications now in preparation. In order to inject massive doses of PVP into dogs without producing an extreme fall in blood pressure which would suppress urine formation, it was necessary to find out whether they could be desensitized. A series of graded doses, with duplication of the final massive dose was successful.

The causes of a disproportionately large decrease in hematocrit value of the second blood samples in a series were found. This was important because the hematocrit value enters into the calculation of renal blood flow measured by clearance methods.

The lack of published corrections for dogs' blood of sedimentation rates at various hematocrit values made it necessary to collect our own. This will make it possible to determine whether an increase in erythrocyte sedimentation rate is due to diluting of to the plasma expander per se.

Significance to NIAMD Research: The significance of this project for the Institute lies in the clarification which may be gained of normal renal hemodynamics, which is the basis for an understanding of pathological conditions. The fact that dogs are sensitive to PVP and not to dextran makes a comparison of these substances an interesting problem in cellular permeability.

Proposed course of project: We do not expect to undertake any major project until the laboratory has moved. Until then, we will be occupied with obtaining normal clearances to be used as baseline values, at the same time accustoming the dogs to the procedure. Renal vein catheterization technique is still to be practiced, and arrangements made for histological studies by ourselves or others.

R.F.O. - 8
December 1981

Analysis of AID Program Activities

Budget Data Sheet

10. STATE- 82129-06
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PROJECT DATA
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1986	17,500	1	2	3	1	2	3	
FY 1988	17,500	1	2	3	1	2	3	

12. BUDGET ENTITY:

REVIEW [X] ACCEPTANCE [ ]

REVIEW & APPROVAL [ ] SUBSEQUENT SUBMISSION [ ]

13. IDENTIFY KEY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OF OTHER ORGANIZATIONS, FOUNDING FUNDS, FACILITIES, OR PERSONNEL NOW (OR WILL SOON) BE UTILIZED IN 1988 or 1988. IF COOPERATING UNIT IS WITHIN SIX MONTHS SERIAL NO. (S)

None

14. IF THIS PROJECT RESPONDS, COINCIDENTS, OR PARALLELS RESEARCH NOW SPONSORED BY THE PUBLIC HEALTH SERVICE (AGENCIES INVOLVED OR PERSONNEL, FACILITIES, FUNDS), IDENTIFY SUCH RESEARCH. (BY SERIAL NO.(S) IF WITHIN SIX)

None

Refer to: 1
Contract [illegible] Institute of the Organic Industries

Report, Project, and Publication Number

16. NIH-G. 5213-06
NIH-11. NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Marshall, L. H. and H. E. Hamm. Differences in 1-1946 and crystalline concentration of venous blood of dogs after Dextran. Am. J. Physiol. 179: (3) 531-534, Dec., 1954.

17. LIST COURSES AND AWARDS TO UNDERGRAD. RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954.

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Physiology
SECTION

4.
LOCATION (IF OTHER THAN DEVELOPED)

5. NIAMD- 62129-07
SERIAL NO.

6. Effects of hypoxia on physiologic mechanisms
PROJECT TITLE

7. Paul D. Altland
PRINCIPAL INVESTIGATOR(S)

8. Edwin C. Thompson
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: Subproject a. Increased erythropoiesis occurs in animals kept repeatedly. Following cobalt administration or as result of exposure to hypoxia but the mechanism of action is unknown. Studies are being conducted using varying degrees of blood clots presumably in order to obtain a better understanding of factors stimulating blood formation. The presence of an humoral (hemotropic) has been postulated as being the primary substance stimulating bone marrow. A search for this substance in dogs is being continued. The longevity of the erythrocyte of various animals is being investigated in order to shed some possible light on the factors responsible for the formation of new erythrocytes.

Subproject b. Repeated exposure of rats to simulated altitude increases their susceptibility to experimental bacterial endocarditis. A method, similar to the one developed by Thomas and Altland for rats, is being developed with larger animals in order to learn more of this common form of heart disease which, despite intensive antibiotic therapy, has a current mortality of 10 to 50%. The influence of hypoxia on the susceptibility of mice to malaria is being studied.

Subproject c. Because of the ever expanding functions of civilian and military aviation, studies on the fundamental mechanisms of natural adaptation to high altitude and of means of increasing hypoxic tolerance by artificial means such as pharmacologic and dietetic are being conducted. Specifically, acclimatization responses of dogs and monkeys and the effects of a high fat diet on altitude acclimatization are being determined.

6. PROJECT DESCRIPTION - CONTINUED

Methods employed: The varying degrees of hypoxia are produced by exposing animals to reduced atmospheric pressures in 2 altitude chambers. Biochemical, hematological, and roentgenological methods are used in the various studies.

Major Findings: Hypoxia, which has been previously thought to act as the fundamental stimulus for erythropoiesis in all vertebrates, has been found to be ineffective as a stimulus to blood formation in cold-blooded animals such as the turtle. Furthermore circulatory and respiratory adjustments to acute exposure to hypoxia, which are characteristic of all homiotherms, are not found in the turtle. A possible explanation for the marked resistance of the turtle erythrocyte to damage by whole-body X-irradiation may be in the finding that the longevity of the turtle erythrocyte is many times longer than any other animal previously reported in the literature.

There is an increased susceptibility of rats to experimental bacterial endocarditis if polycythemia is prevented by repeated bleedings during the period of exposure to altitude. The resistance of rats is not lessened by a diet containing cobalt, which produces polycythemia but not hypoxia. These findings suggest that polycythemia acts by increasing the work load of the heart and that hypoxia lowers the resistance to certain bacteria, and that both such factors are needed to render a normal heart more susceptible to infection.

Significance to [illegible] Research: Provides information for a better understanding of the relationship of metabolism and blood formation. Supplying a method for examining various factors important in the development and treatment of cardiovascular diseases.

Proposed course of project: Attempts will be made to find a cold-reacting animal representative of a class other than reptiles to be used to provide further data on the relation of hypoxia to blood formation and physiologic adaptations. Preliminary evidence and suggests that it is possible that erythrocyte longevity may be correlated with species longevity in poikilotherms. Studies will be conducted under to substantiate this hypothesis.

Further attempts will be made to render dogs susceptible to experimental bacterial endocarditis for the purpose of providing a tool for the surgical, physiological and therapeutic studies. Further attempts to influence the course of experimental malaria will be considered. Various strains of mice found to show marked variation in their erythropoietic response to hypoxia.

Work will continue on the in vivo production of erythropoietin in [illegible]

The studies on the altitude acclimatization of mouse cells will be continued, and the subject of factors affecting altitude tolerance is being thoroughly explored.

N.I.H. - E
Rev. August 1960

10. NIAMD - 62132-67
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	SALARY AND WAGE
FY 1966	23,300	1	3	4	1	3	4	
FY 1968	23,300	1	3	4	1	3	4	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

NIH/PHS A APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OR THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR SERVICES FOR THIS PROJECT (STATE: NONE OR NAME OF COOPERATING UNIT IN WHICH MIH EMPLOYEE SERIAL NO(S) LOCATED)

Studies on longevity of erythrocytes are being conducted with cooperation of Dr. Margaret Green of General Radiobiology Section, National Cancer Institute, NIAMD -

Studies on hemocoprosterin in dogs conducted in cooperation with Drs. Charles G. Sinn, Paul Hogan, and G. Leonard Cooley of the Department of Medicine of The Johns Hopkins Hospital, Baltimore, Maryland.

Endocarditis studies conducted with cooperation of Dr. Benjamin Highman of Section on Pathologic Anatomy, NIAMD - 62112-62

Studies with mouse animals are being conducted with cooperation of Dr. Olaf Mickelsen of Section on Biochemistry and Physiology of Nutrition, NIAMD. NIAMD-62113-12

14. IF THIS PROJECT REPEATS, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

D.P.S. - 1
Research 18-a Analysis of the oxygen deficiency

Honors, Awards, and Publications Sheet

18. NIAMD. 62129-37
SURGEN GI.

26. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1964:

Altland, P. D. and R. Highman. Effect of a folic acid antagonist (Pteroyl PGA) upon rats exposed to high altitude. Am. J. Physiol., 176: (3) 1-4, Jan., 1954.

Altland, P. D. and M. Fechter. Effects of hypoxia upon the bone marrow. Accepted by Am. J. Physiol.

Highman, R., P. D. Altland and H. Wagle. Experimental bacterial endocarditis in altitude rats. AMA Arch. Path., 58: 241-257, Sept., 1954.

17. LIST NUMBER AND NAMES OF PERSONNEL PAID TO WORK ON THIS PROJECT DURING CALENDAR YEAR 1954:

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR BRANCH

3. Embryology
SECTION

4.
LOCATION (IF OTHER THAN BUILDING)

5. NIAMD-63(29-63
SERIAL NO.

6. To investigate the metabolic responses to stress and to drugs of human cells and tissues
PROJECT TITLE

7. Frederick Sperling
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: Tagging the cellular components (RNA, proteins, carbohydrates, nucleic acids, etc.) with C^{14} and analysing the changes in the C^{14} and analysing the changes in the C^{14} contents of these components after exposure to drugs and to stress.

Methods Employed: The primary components (fats, proteins, etc.) of the eggs were made radioactive by injecting the female with formaldehyde. Ovulation was then induced by pituitary injection, and the eggs fertilized in a sperm suspension. These eggs were chosen because they are completely self-sufficient in terms of food; represent a generalized cell type rather than a specialized cell type for a short developing period of time during development; are easily tagged; and are readily obtainable in large numbers.

The fertilized eggs are exposed to such drugs as diethylstilbestrol and allowed to develop to pre-determined stages. Controls receive no diethylstilbestrol, and during the same developmental stages are used for comparison. At the various stages of development, control and experimental eggs and embryos are removed, and the constituent components extracted, analysed and compared.

9. PROJECT DESCRIPTION - CONTINUED

Major findings: The development of standard methods for permitting direct comparison of C^{14} activities between control and experimental eggs and embryos.

In terms of changes in C^{14} during various developmental stages it has been found that C^{14} activity in fats begins to drop just after cleavage begins, but that C^{14} activity in proteins remains the same for a long period of development. When the eggs are exposed to 0.2% dextrose, the drop in C^{14} activity in the fats is less than that of the controls, while the proteins remain at the same level as the controls, and show no change. When exposed to $1:1,000,000$ dilution of dinitrophenol, the C^{14} activity of the fats drops more sharply than the controls, and the C^{14} activity of the proteins shows a sharp decline which is absent in the controls and in the dextrose-treated group. During these developmental stages, there is no apparent decline, in both controls and experimental embryos, in the weights of either the fats or the proteins.

Significance to NIAMD Research: In order to understand the internal responses of cells and tissues to drugs and to stress and thus the effects of drugs and stress on an organism, the changes occurring within the cells and tissues must be thoroughly analyzed. The methods discussed above appear to be able to supplement and enhance information obtainable by other physiological, pharmacological, biochemical and physical methods.

Proposed course of project: Further refinements of methods are indicated as well as the isolation and analysis of total C^{14} changes in C^{14} activity of the various amino acids and lipid units. The changes in these may indicate the mechanism whereby normal changes in C^{14} activity in proteins occurs without apparent weight change, after exposure to dinitrophenol.

9. PROJECT DESCRIPTION - CONTINUED

Major Findings: The development of standard methods for permitting direct comparison of C^{14} activities between control and experimental eggs and embryos.

In terms of changes in C^{14} during various developmental stages it has been found that C^{14} activity in fats begins to drop out after cleavage begins, but that C^{14} activity in proteins remains the same for a long period of development. When the eggs are exposed to 0.2% dextrose, the drop in C^{14} activity in the fats is less than that of the controls, while the proteins remain at the same level as the controls, and show no change. When exposed to 1:1,000,000 dilution of dinitrophenol, the C^{14} activity of the fats drops more sharply than the controls, and the C^{14} activity of the proteins shows a sharp decline which is absent in the controls and in the dextrose-treated group. During these developmental stages, there is no apparent decline, in both controls and experimental embryos, in the weights of either the fats or the proteins.

Significance to NIAMD Research: In order to understand the internal responses of cells and tissues to drugs and to stress and thus the effects of drugs and stress on an organism, the changes occurring within the cells and tissues must be thoroughly analyzed. The methods discussed above appear to be able to supplement and augment information obtainable by other physiological, pharmacological, biochemical and physical methods.

Proposed course of project: Further refinements of methods and techniques as well as the isolation and analysis in terms of changes in C^{14} activity of the various amino acids and [illegible]. The changes in these may indicate the mechanism whereby normal changes in C^{14} activity in proteins occurs without apparent weight change, after exposure to dinitrophenol.

10. [illegible]

11. [illegible]

	[illegible]	[illegible]			[illegible]			[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
FY 1985	7,300	1		1	1		0	
FY 1986	7,700	1		1	1		1	

12. [illegible]

[illegible] [illegible]

13. [illegible]

None

14. [illegible]

None

B.P.C. - 5
December 1964

Animal Cell Organ Activities

Personnel, Awards, and Publications Sheet

15. Project 02130-03
Period Ending

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS AND THOSE SHOWN DURING CALENDAR YEAR 1964.

Sperling, F. Electron-probe autoradiography of radioactive frog embryos. Nature, 1964; 748, Oct. 10, 1964.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO NIH PROJECT DURING CALENDAR YEAR 1964.

None.

1. Rabbit muscles of cellulose and catalytic hexoses
INSTITUTE

2. Laboratory of Physical Biology
LABORATORY OR SERVICE

3. Synaptic Biochemistry
SECTION

4. _____
LOCATION (IF OTHER THAN ADDRESS)

5. [illegible]
ANNUAL NO.

6. The mechanism of the orderly aggregation of proteins in building up biological structures
PROJECT TITLE

7. Dr. Solomon Leid and Dr. E. S. Williams
PRINCIPAL INVESTIGATOR(S)

Dr. V. J. Brown	E. L. Lewis	Fredric M. Rose
Dr. D. M. Deamer	W. J. Williams	Margot O. Thomas
Dr. W. H. Connell	B. T. Evans	C. E. Weeks
Dr. V. A. Ewell	[illegible]	
Dr. L. M. Simpson	[illegible]	

8. Dr. F. Ironmonger
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to study the composition of polymerizations of proteins in order to help workers as to how cells build up cellular structures. The processes involved in muscular contraction and blood coagulation are the results of protein polymerizations. The main part of this project is, therefore, devoted to the study of proteins involved in muscular contraction and blood coagulation.

Methods Employed: The method of attack is both direct and indirect. In the direct attack the proteins of muscular contraction or blood coagulation are separated from their native milieu and are studied under arbitrary conditions which are selected to reveal properties of interest. (Including) characterization: size and shape of the molecules, determination of chemical composition, modifications brought about by changing specific groupings either chemically or enzymatically.) In the indirect attack studies are made on some other already better known proteins to

9. PROJECT DESCRIPTION - CONTINUED:

gain information before the direct attack is made (e.g. acetylation of serum albumin or a study of antigen-antibody reaction). In these studies the procedures of biochemistry and physico-chemistry are employed. For example: paper and ion-exchange chromatography, enzymology, ultracentrifugal analysis, osmometry, light-scattering measurements, electrophoresis, the diffusion measurements, etc.

Major Findings: It was further demonstrated that ATP-splitting and contraction of muscle fibers are not correlated (Szent-Györgyi) and it was found that besides ATP and Ca^{++}, inorganic salts (KCl), F (known to depolymerize actin), cause muscle fibers and myosin-F threads to contract (Hoh, Hasan).

It was observed that both human and bovine serum albumin can be induced to polymerize reversibly under the influence of inorganic ions and salts (Haroff). Some interesting binding constants have been measured in connection with the interaction of proteins and metal ions, and it was shown that copper ions dissolve serum albumin (Haroff, Hagopian).

A quantitative determination of the amino acid composition of the two peptide components of α-fibrin has been achieved. It was found that guanidinated lysine is eluted by threonine and that the α-fibrin released also contains guanidinated amino acids (Lehr, Haskins, Haroff).

The presence of the amino acid lysine (which its amino group normal) was discovered in the protein-solvent (Haskins).

Gelatin was found to be heterogeneous from the chemical point of view in spite of its homogeneous appearance in physico-chemical measurements (Carroll, Rhodes).

It was further demonstrated by using ninhydrin and gelatin that D-amino-isa-urea is a isotopic new reagent to react with amino and groups in proteins (Haroff, Hirabayashi, Fruton).

A peptide was found in human γ-globulin preparations which inhibited the agglutinin reaction characteristic for rheumatoid arthritis patients (Williams).

Significance to NIAMD Research: When part of the protoplasm or the whole cell (as in, e.g., cell division or muscular contraction) performs mechanical work, a network structure is built up at least temporarily, mainly through an orderly polymerization of globular proteins. This structure then reacts with the surrounding material and by

utilizing metabolic energy (stored in ATP e.g.) performed work (muscular contraction, amoeboid movement). In order to understand this "energy-coupled coupling" (the interaction of structure with the surrounding) and the <u>dynamics</u>, we must know how such structures are built up. Muscular contraction and blood clotting are examples of processes where structures are built up through covalent polymerization. Such knowledge eventually will lead us to the understanding of certain diseases of muscle. Study of blood clotting, in addition to supplying clues for protein polymerization, gives us better understanding of the disorders of blood clotting (like hemophilia).

When both direct and indirect approach leads to some specific disease (e.g. hemophilia, rheumatoid arthritis) the advantage offered by studying the disease is outlined to the extent profitable.

<u>Proposed course of project:</u> In the next calendar year the project will be pursued along the lines outlined above. It is further planned that a study on hemophilia will include a study of the clotting defect of a hemophilic patient. The possible physiological role of co-fibrin will be investigated. The partial analysis of the amino acid sequence of one of the peptides of co-fibrin is planned, together with a search for an enzyme which split off the tyrosine-basal sulfate from the peptides. Hydrodynamical studies will be further extended to study the effect of temperature on the two conformations of myosin. The usefulness of o-acetyl-iso-urea as an end-group reagent will be further investigated and the epimerization reaction of rhamnose pathway will be studied further.

10. NIAMD- 62130-90
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT BEDS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	144,300	12	13	25	12	12	24	
FY 1956	147,300	12	13	25	12	13	25	

12. BUDGET ACTIVITY:

RESEARCH ☑ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL 1955 or 1956. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (Type)

Dr. Harold A. Scheraga, Department of Chemistry, Cornell University, Ithaca, New York.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

A.F.S. 1.1
December 1954 Progress of the research activities

Reports, Lectures, and Publications Staff

13. NT 110 c 621.30-50
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Bower, V. E., and Kerwin, P. D.: The kinetics of myosinase. I. Studies of the effects of salts and pH and of the state of equilibrium. Arch. Biochem. Biophys., 49: (2) 349-359, Mar., 1954.

Irreverre, F., and Martin, W. L.: Versatile technique of paper chromatography. Anal. Chem., 26: 297, Feb., 1954.

Mommaerts, W. F. H. M., Haugh, A., Symonds, V., and Lehl, K.: The amino acid composition of actin, myosin, tropomyosin and the nucleoprotein. Arch. Biochem. Biophys., 50: (2) 348-357, May, 1954.

Lehl, K., Haugh, A. E., Symonds, P., Lenard, L., and Seegers, W. H.: The amino acid composition of bovine prothrombin. Arch. Biochem. Biophys., 49: (1), 279-282, Jan., 1954.

Lenard, L. and Lehl, K.: A simple method for purifying an activator of prothrombin (antihemophilic factor). Biochim. Biophys. Acta, 13, [illegible] 1954.

Sarett, H. A.: Diffusion Apparatus. Patent 2675247, Apr. 13, 1954.

Prince, E. T., Morales, M. F., and Scott, W. J.: Some further observations on the interaction of DNA with the myosin-ATP system. Arch. Biochem. Biophys., 51: (1) 111-112, Dec., 1954.

Kerwin, P. D., and Kerwin, P. D.: A study of the effects of ethylenediamine tetraacetic acid on myosin ATP-ase. J. Biol. Chem., 211: (1) 257-267, Nov., 1954.

Schwarz, H. A., Carroll, W. R., Mims, L. F., Sutton, H., Easton, J. T., and Saunders, J. H.: Hydrodynamic properties of urea-denatured fibrinogen. J. Polymer Sci., 14: (77) 447-460, Nov., 1954.

Lehl, K.: The chemistry of prothrombin and some of its reactions. Physiol. Rev., 34: (4) 710-715, Oct., 1954.

Edsall, D. E., Geyssy, H. H., Simpson, H. B., and Stavenau, E.: Determination of serum sarcoplasmin in presence of mercurials. II. Studies with a difunctional organic mercurial. J. Am. Chem. Soc., 76: 3131 (1954).

16. PUBLICATIONS - CONTINUED

Brimhall, G. A., Jr., Andreasen, L. E., Cleeton, J. L., Clegg, J., and Carroll, W. R.: Studies on the prosthetic groups, amino-histidine, and terminal sequences in ribonuclease. J. Biol. Chem., 207: 533, 1954.

Ledd, K., and Green, M. J.: The contraction of muscle fiber and myosin B thread in KI and KSCN solutions. To appear in Biochim. Biophys. Acta.

Simpson, S. E., Green, M. J., and Ruoff, H. A.: Polarography of the noble metals. To appear in March 1955 Jour. of Am. Chem. Soc.

Dunn, J. J., Sokoloff, L., Williams, E. D., and Ehrich, W. E.: Rheumatoid arthritis: A review of recent advances in our knowledge concerning its pathology, diagnosis and treatment. To appear in Feb. 1955 issue of Jour. of Chronic Diseases, Vol. 1, No. 2.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases

2. Clinical Investigations
LABORATORY

3. Arthritis and Rheumatism
BRANCH

4. Bethesda
LOCATION

5. NIAMD - 62131-03
SERIAL NUMBER

6. The Nature of the Anemia of Rheumatoid Arthritis
PROJECT TITLE

7. Franklin G. Ebaugh, Jr., M.D.
PRINCIPAL INVESTIGATOR

8. Ralph E. Peterson, M.D., Gerald P. Rodnan, M.D., Joseph J. Annis, M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To afford an understanding of the reasons why certain patients with active rheumatoid arthritis become anemic.

Methods Employed: The measurement of the duration of circulating erythrocyte life span in patients utilizing the simple Selective agglutination technique and radioactive Sodium Chromate labeled red blood cells; determinations of serum copper and the determination of the rate of plasma iron clearance and the subsequent rate of utilization of iron by the bone marrow to make erythrocytes by radioactive Fe-59 tracer techniques and the chemical determination of the serum iron; the measurement of the rate of excretion in the feces of urobilinogen and bloodstream bilirubin levels; and concurrent clinical studies on the natural course of the anemia and the effect of certain therapeutic agents on the course of the anemia.

Patient Material:

		No.	Average Red Blood Cell Life Span
Admissions:	Adult males	0	
	Adult females	10	
	Children male	1	
	Children female	2	
Outpatients:	Number of patients	7	
	Number of visits	21	

Major Findings: The mean red blood life span in a series of patients was determined and found in the majority of patients are to be significantly shortened from a comparable group of normal males and females. The dynamics of iron metabolism were studied in a number

of patients and the rate of hemoglobin production was low. The serum iron was found to be low in most patients. The administration of iron orally or intravenously did not significantly increase the serum iron or the red blood cell counts. Thus it is concluded that a deficiency of body iron is not the cause of the anemia. An abnormal type of purine metabolism not previously described has been found to occur in arthritic patients. A new method has been developed for the determination of serum copper.

The beneficial effect of steroid therapy in the control of arthritis, described previously by others, has been confirmed, although the mechanism whereby steroids control the arthritis is apparently not understood, some progress in this problem has been made by studies presently in progress.

Significance to NIAMD Research: This study is but one of several long term projects whose aim is to understand more fully the cause of rheumatoid arthritis and its cure. This project illustrates progress in a clinical and laboratory study of the control of the arthritis of rheumatoid arthritis. It is doubtfully likely that by no means a certainty that a more complete understanding of the mechanism of the control of arthritis will lead to clinically useful in discoveries of the cause of arthritis.

Proposed Course of Project: Studies concerning the mechanism of steroid control on the arthritis will be continued as well as investigations designed to more fully characterize the defect in purine metabolism demonstrated in the current studies.

10. NIAID - 5Z01-91
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			DAY CLERK			PROFESSIONAL SERVICES
		PHYS	OTHER	TOTAL	PHYS	OTHER	TOTAL	
FY 1955	23,100	2	1	3	1 1/3	1	2 1/3	USDC
FY 1956	25,000	2	1	3	2	1	3	USDC

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S)

None

14. IF THIS PROJECT DUPLICATES, COMPLEMENTS, OR PARALLELS RESEARCH NOW UNDERWAY IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

15. NIAMD - 62131-01
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING THE YEAR 1954:

Peterson, E.E., and Sallier, R. The Determination of Serum Copper with bis-Cyclohexanone-Oxalyldihydrazone. Anal. Chem., In press.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING THE YEAR 1954:

None

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations
LABORATORY

3. Arthritis and Rheumatism
BRANCH

4. Bethesda
LOCATION

5. NIAMD-A2131-02
ZERIAL NUMBER

6. Iron Metabolism in Man, in Health and Disease
PROJECT TITLE

7. R. E. Peterson
PRINCIPAL INVESTIGATOR

8. O. Rodnan; F. Hamagh; M. Heller
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objectives of this project are the study of oral iron absorption in patients with liver disease and patients with various anemias and determination of the turnover rate of iron in the normal male and female, and in patients with various hematological disorders.

Methods Employed: Oral iron absorption is determined by feeding a known quantity of radioactive ferric salt and determining the per cent absorbed and the per cent incorporated into the red cells. Iron turnover rate is also determined by the use of radioactive iron.

Patient Material:

		No.	Average Stay (Days)
Admissions:	Adult males	12	21
	Adult females	20	20
	Children	0	0
Outpatients:	Number of patients	20	
	Number of visits	130	

Major Findings: Studies to date seem to indicate that patients with liver disease and patients with certain anemias absorb more iron than normal subjects; however, a final evaluation of this data must await additional studies on normal male and female subjects.

The studies on iron turnover rate show an average figure of 0.30 mg/kilo/day in the normal female, and a similar figure for the

9. PROJECT DESCRIPTION - Continued

normal male. However, the few studies with normal males have been made to state that there is no significant sex difference. A number of more than 100 studies have been carried out in psychosis with various anemias, and it appears that the iron turnover rate is not always directly correlated with the rate of hemoglobin production.

Significance to NIAMD Research: The studies on iron absorption are of significance as related to the problem of the pathogenesis of siderosis (iron storage disease). The studies on iron turnover are directed towards an evaluation of this method as a simple procedure for investigating hemoglobin synthesis in vivo.

Proposed Course of Project: Additional studies of iron absorption in normals should be carried out, as a "prelude" to studies in the finding in disease. Also, additional iron turnover rate studies must be carried out in normal males. Thereafter work will be further evaluated in various disease states.

N.P.L. - C
December 1954

10. MH-NIB-5213-C2
CHRIA, Norman

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	PROFESSIONAL PERSONNEL			NON-PROFESSIONAL PERSONNEL			PERCENT TIME
		FULL-TIME	PART-TIME	TOTAL	FULL-TIME	PART-TIME	TOTAL	
FY 1955	16,700	1	1	2	1	1 1/5	2 1/5	100
FY 1956	17,000	1	2	3	1	1 1/2	2 1/2	500

12. BUDGET ACTIVITY:

ORIGINAL ☒ AUGMENTATION ☐

RENEWAL & APPROVAL ☐ SUPPLEMENTAL ALLOWANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL 1955 or 1956. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

Georgetown University Hospital

14. IF THIS PROJECT RESEMBLES, DUPLICATES, OR PARALLELS RESEARCH BEING SUPPORTED IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

Analysis of the Present Investments
Interest, Dividend, and Publications Income

25. NYW 40150-42
Shelf: 707/3

26. List publications other than abstracts that issued during calendar year 1954:

None

27. List honors and awards to personnel relating to this project during calendar year 1954:

None

1. National Institute of Arthritis and Metabolic Diseases

2. Clinical Investigation
LABORATORY

3. Metabolic Diseases
BRANCH

4. Bethesda
TERRITORY

5. NIH - 6213-22
NIH NUMBER

6. Studies of Purine Metabolites in Gout
PROJECT TITLE

7. James B. Wyngaarden, Stanton Segal, Leonard Lasker, and J.F. Seegmiller
PRINCIPAL INVESTIGATORS

8. Lois Liddle and Alberta Hirsi
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To gain understanding of clinical gout by studying uric acid biosynthesis and excretion in normal and gouty subjects, and by investigating the mechanism of action of drugs which influence these factors.

Methods Employed: The incorporation of isotope from orally administered precursors into various purine excretion products was studied in normal and gouty subjects. Uric acid conversion in patients with various stages of gout, and the effect of drugs on this excretion were investigated. The serum and urin of patients were assayed with enzymatic and chromatographic methods for compounds related to purine metabolism. Pigeon liver homogenates were used in an in vitro study of pathways of uric acid biosynthesis.

Major Findings: In confirmation of our previous studies, in a normal subject L-serine-β-C^{14}-3-hydroxydicarboxylic-d^{15} was again incorporation uric acid by the metabolic pathways and also demonstrated the incorporation of glycine-C^{14} into uric acid, suggesting an inhibition of the de novo synthesis of purines from glycine. In absence of isotope dilution of L-serine-β-hydroxydicarboxylic (HDC) recovered form urine during the study indicated that there is no rapidly miscible pool of this compound in body fluids. The incorporation of HDC into uric acid in one gouty patient studied was greater than normal.

Phenylbutazone, a drug which lowers plasma uric acid levels, was shown to act solely as a uricosuric agent, having no effect on rates of synthesis or of catabolism of uric acid. Intravenous, a sodium

[illegible] injection, was known to affect only a single reaction of uric conversion into gives in rear-wrinkle cocks. Theophylline, a[illegible] agent, was given to be relatively ineffective and could damage [illegible] serum.

[illegible] report that [illegible] levels were [illegible] but [illegible] corporine levels very high is gone was not confirmed. Normal [illegible] of low purine diets were given to control patients, hypoxanthine, adenine, guanine and 6-methyl purine in 0.5 - 30 mg. quantities daily.

Significance to NIAMD Research: We have shown that in the human, as in [illegible] biological systems, AIR is a precursor of uric acid, although the presence as a normal intermediate in purine metabolism has not been demonstrated. This compound can now be used to study claimed conditions involving abnormalities of purine metabolism. The finding that AIR can appear may be more evidence of purines in the human suggests new fields of investigation of the factors involved in the regulation of purine production.

The mechanism of action of drugs useful in the treatment of gout has been further elucidated. The role of 7-methyl guanine in purine metabolism is not known and remains to be investigated.

Proposed Course of Project: Studies with labeled AIR will be continued to [illegible] a variety of clinical conditions in which hyperuricemia is found. The mechanism by which AIR exerts its action on purine biosynthesis will be investigated. Patients are being [illegible] for a study of the conversion of possible metabolic precursors of purines in patients with gout. Patients will be investigated for precipitating factors of episodes of acute gout and for variations in uric acid excretion during the course of their disease.

The question of whether or not overproduction of uric acid in gout involves nucleic acid pathways or a more direct route is currently under investigation by means of a study of the [illegible] of 2-carbamoyl of urinary purines (adenine, guanine, 7-methyl guanine, hypoxanthine, xanthine and uric acid) following glycine-2-[illegible] The validity of equating urinary adenine and guanine excretion with that of nucleic acids is being evaluated by means of periodic sampling of white cell nucleic acid purine activity.

Studies of early intermediates in purine synthesis are being continued in pigeon liver enzyme systems.

10. [illegible]
SOCIAL SECURITY

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	DESIRED POSITIONS			MAN YEARS			OTHER DATA
		P-5/6	OTHER	TOTAL	P-5/6	OTHER	TOTAL	
FY 1955	53,400	1	4 1/2	5½	1 1/2	4½	6	30C
FY 1956	61,000	4	5	9	4	4½	5½	30C

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]
REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. [illegible]

Section on Interviewing Methodology, LMN, NIAMD - [illegible]

14. IF THIS PROJECT [illegible]

None

December 1954

15. NIAMD - 642.91-93
SERIAL NUMBER:

16. LIST PUBLICATIONS (WHICH HAVE RESULTED FROM THIS PROJECT DURING CALENDAR YEAR 1954):

The Effect of Phenylbutazone on Uric Acid Metabolism in Two Normal Subjects. James B. Wyngaarden. J. Clin. Investigation. In Press.

Uric Acid. James B. Wyngaarden, in G.M. Piersol, Cyclopedia of Medicine, Surgery, and Specialties, F.A. Davis and Co. Philadelphia, In Press.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

Analysis of ICP Program Activities

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations 6 3. Arthritis and Rheumatism
LOCATION DIVISION

4. Bethesda 7. AM-04231-04
LOCATION GRANT NUMBER

6. Studies on New Antirheumatic Steroids
PROJECT TITLE

7. Joseph J. Burns, Alfred J. Solleg, Roger Black
PRINCIPAL INVESTIGATORS

8. NONE
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The great discrepancy of present methods of treatment of rheumatoid arthritis has resulted in a search for new drugs which might be of therapeutic value. In view of the useful, though inadequate, action of steroids that are now in use, other steroid compounds are being sought which might have greater value. The present study aims to determine if new steroids which have been synthesized have greater therapeutic usefulness by reason of greater anti-rheumatic potency with fewer side-effects.

Methods Employed: Studies have been in progress at NIAMD concerning the new steroids, medrysone (HMS) and prednisolone, particularly the following comparison. The effect of these drugs in rheumatoid arthritis has been evaluated by administering them to patients, after suitable control observations, and carefully noting changes in symptoms, joint changes, functional capacity, tissue pathology, and blood constituents. The symptomatic changes are observed after careful questioning of the patient. Joint changes are noted by careful examination of every joint, recording each type of finding by means of a numerical code, and then quantitating the severity of these changes by means of this code. The functional state of each patient is observed by means of careful measurement of the range of motion of each joint, expressing the total abnormality in range of motion as a percentage of normal. Tissue changes are observed by means of biopsies of synovial or other tissues. Changes in the ESR, 0-reactive protein, serum proteins, serum electrolytes, cholesterol, calcium, phosphorus, hemoglobin, white blood cells and circulating eosinophiles are also checked. Hormonal effects of these drugs are observed by means of the above tests, plus observations on excretion of 17-keto-steroids.

PROJECT DESCRIPTION - Continued

Studies in progress include the effectiveness of these drugs in rheumatoid arthritis, both on a short-term basis and as long-term therapy. Careful metabolic balance studies are being conducted to observe the effect of the drugs on electrolyte, nitrogen, calcium, phosphorus and water metabolism. Pharmacologic studies of the rate of disappearance of these steroids from the blood and excretion in the urine are under way, and, studies of their clinical effectiveness in other rheumatic diseases, especially lupus erythematosus.

Major Findings: Results thus far have indicated that these drugs have potent antirheumatic and anti-inflammatory effects, several times more potent than cortisone and hydrocortisone. Patients experience dramatic relief of pain, increase in functional capacity, subsidence of the manifestations of joint inflammation, with marked clearing of the acute inflammatory changes in the tissues and changes in the nerve electrical titles. In addition the drugs have been observed to have potent pituitary hormone actions, inducing eosinopenia and fall in excretion of 17-ketosteroids. They also induce a fall in serum fibrolin and a rise in serum cholesterol. These drugs did not cause salt and water retention, one of the main side effects of cortisone. They do cause a loss of nitrogen, but this is not as great as with previous steroids.

Many side-effects have been observed with these drugs, including hirsutism, menstrual irregularities, acne, enhanced libido, and some mental clouding. No serious side-effects definitely attributable to these drugs have been observed as yet. Some tendency for the effectiveness of the drug to diminish after prolonged administration has been noted, but this has not been observed sufficiently to determine how seriously it will impair the usefulness of the drugs.

Significance to NIAMD Research: This study has given reason to hope for significant advances in the treatment of rheumatoid arthritis and other rheumatic diseases in the near future. The drugs currently under investigation have been found to be potent agents, without some of the serious side-effects of previous steroids. Their final value and place in the treatment of the rheumatic diseases remains to be worked out, but it seems certain that they will be of some importance. These results also give encouragement that similar modifications of the basic steroids will result in more useful drugs.

Proposed Course of Project: It is planned to continue the present line of investigation of these new steroids in order to determine what their effectiveness is and what role they may play in the treatment of rheumatoid arthritis and the other rheumatic diseases. Specifically, the problem of adequate dosage and treatment schedules is being worked out, side-effects are being carefully noted and means of avoiding them studied, the development of resistance to the effects of the drug is being carefully investigated. Similar studies are under way in lupus erythematosus and scleroderma and these will be enlarged, and repeated with other rheumatic diseases.

10. WIAMD-621.31-54
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	EMPLOYEE POSITIONS			MAN YEARS			AVERAGE SALARY
		U.S.	OTHER	TOTAL	U.S.	OTHER	TOTAL	
FY 1955	21,300	2	1/3	2 1/3	2 5/6	1/3	2 1/3	1200
FY 1956	22,000	2	1	3	2	1/2	2 1/2	1200

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

TRAINING [ ] OPERATIONS [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY CONTEMPLATED USES OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL 1955 or 1956: (IT CONSIDERED NOT IN VIOLATION FOR INDIANA SERIAL NOS.)

Dr. Maurice Pechet - National Heart Institute

14. IF THIS PROJECT ASSEMBLES, CONSIDERS, OR VITALIZES RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN PHS)

None

Nursery, Research, and Publication Branch

15. NIAMD-SCLM-84
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Observations on the Anti-Rheumatic Potency, Metabolic Effects and Toxicity Properties of Some Synthetic Steroids, Neurocortandralone and Desoxycortandralone. Presented at ARA Meeting 11/4/54 and in Press J.A.M.A.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATED TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations
LABORATORY

3. Arthritis and Rheumatism
BRANCH

4. Bethesda
LOCATION

5. NIAMD - 62131-05
SERIAL NUMBER

6. Studies of Mucopolysaccharides and other Components of Connective Tissue in Rheumatic and other Diseases, and of similar Components in Blood, Urine and Synovial Fluid.
PROJECT TITLE

7. Alfred Jay Cottieb, Norman Rose
PRINCIPAL INVESTIGATORS

8. Joseph Foley, Mary B. Coppoloch
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To investigate alterations of mucopolysaccharide structure and [illegible] metabolism in response to various pathological states.

Methods Employed: The biosynthesis of hexosamine has been studied [illegible] rats on a hexosamine free diet and in vitro using [illegible] of rabbit connective tissue grown in tissue culture. The effect of thyroidectomy and hypophysectomy on the concentration of hexosamine in fat pleura and connective tissue has been investigated. Paper electrophoresis has been used to separate components of normal connective tissue and the hexosamine content of various fractions was determined. In human studies the effect of sulfonamides on the hexosamine content of connective tissue has been studied and the effect of stress, ACTH administration and various pathological states on concentration of hexosamine in blood and urine has been investigated.

The intrinsic viscosity of synovial fluid from patients with various rheumatic diseases has been determined as part of a study of abnormalities of hyaluronic acid in pathological states.

Major Findings: The major findings of these studies include the observation that the intact animal suffers no loss of carbon [illegible] a hexosamine-free diet, that rabbit connective tissue can synthesize hexosamine in vitro, that thyroidectomy and hypophysectomy cause changes in connective tissue and blood hexosamine levels (hypophysectomy raising the levels and hypophysectomy preventing the effect of thyroidectomy). Serum proteins were found in abundance in blood. Lipid extracts of connective tissue, and the hexosamine in connective tissue was found to be divided between protein and mucopolysaccharide components of connective tissue about equally. The hexosamine and water content of the skin and subcutaneous tissues of patients with [illegible]

...serum were found to be ...ribed compared to normal controls. The ...crease of ...ctivity in the urine was found to be ...ly ...in normal individuals on a day-to-day basis, and this level was found to become elevated by clinical stress of any type, whether and relation to the kind of disease process. ACTH did not cause an ...in serum or urinary hexuronic, ruling out the pituitary as the ...in this response. The hyaluronic acid of the synovial fluid of patients with rheumatoid arthritis was found to be depolymerized compared to normals and to patients with other rheumatic diseases. This depolymerization was not related to the degree of inflammation of the joint, the duration, stage or severity of the arthritis, the ... of cartilage destruction as determined radiologically, and was not reversed by any type of steroid therapy in spite of marked reduction of the inflammatory reaction as a result of therapy.

Significance to NIAMD Research: These studies throw light upon basic ... of connective tissue metabolism and physiology in health and disease, giving us information concerning the ... of the synthetic activities of connective tissue, how these processes are controlled by hormones and why changes appear during ... disease. They also give information concerning the nature of ... of the changes observed in disease processes, and may lead to a better understanding of the pathogenesis of certain rheumatic diseases, especially rheumatoid arthritis. New techniques have been ... during the course of these studies, which may help provide more information along these lines.

Proposed Course of Project: At the present time studies are continuing on the nature of the hyaluronic acid in synovial fluid in different diseases, in an attempt to determine the ... bringing about the changes observed, and the significance of these changes. A search is being made for a possible enzyme which might depolymerize the hyaluronic acid in synovial fluid, to see if ... in the activity of such an enzyme could be responsible for the ... abnormalities observed. The fact that synovial fluid hyaluronic acid is linked in a complex to protein has been demonstrated recently by means of the analytical ultracentrifuge, and studies are continuing concerning the nature of this protein, the amount of its ... to the hyaluronic acid in various joint diseases, and what relation it ... to the observed changes in the mucopolysaccharide. It is also planned to study the synthesis of hyaluronic acid by connective tissue by means of the tissue culture technique ... earlier.

10. GRAND - 62132-95
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PERSONNEL COST
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	21,350	1	2½	3½	1	2½	3½	20,0
FY 1956	28,000	2	3	5	2	4½	6½	26,0

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY CONSULTED UNITS OF THE PUBLIC HEALTH SERVICE OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1955 or 1956: IF CONSULTATION HAS NOT BEEN HELD INDICATE SERIAL NO. IF

None

14. IF THIS PROJECT ASSEMBLES, DEVELOPS OR DISTRIBUTES MATERIALS USED IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL), EXPLAIN IN DETAIL; IDENTIFY SUCH MATERIALS: (SEE SPECIAL NO. 191 FOR DETAILED INFO)

None

15. NIAMD - 62131-05
SERIAL NUMBER

16. LIST PUBLICATIONS ORIGINATING FROM THIS RESEARCH PROJECT DURING CALENDAR YEAR 1954:

Synthesis of Hexosamine by Connective tissue (in vitro) Science 1954
Bottet, Rose and Rubin

Effects of Growth, Fasting, and Trauma on Concentration of Connective tissue Hexosamine and Water. Rose and Foley. P.S.E.B.M. 1954.

Regulation of Connective tissue Hexosamine Levels by the Anterior Pituitary and Thyroid Glands. Rose and Foley. P.S.E.B.M. 1954

Effect of Thyroidectomy and Hypophysectomy on Plasma Hexosamine Level in the rats. Rose and Foley. Endocrinology. (in press)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations
LABORATORY

3. Arthritis and Rheumatism
BRANCH

4. Bethesda
LOCATION

5. NIAMD - 62 J1-06
SERIAL NUMBER

6. Physiological, Pharmacological and Enzymological Studies on Corticosteroids, Cortisone, Hydrocortisone, Radioactive Hydrocortisone.
PROJECT TITLE

7. E.C. Peterson, J.S. Hyngstrom, K.J. Isselbacher and J.J. Bunim
PRINCIPAL INVESTIGATORS

8. Charles Pierce, Margaret Collier, and F. Michael
OTHER INVESTIGATORS

9. PROGRESS DESCRIPTION

Objectives: The following are the main objectives of this project: 1) [illegible] ology and physiological disposition of hydrocortisone, cortisone and corticosterone in man and animals. 2) Metabolic transformation of hydrocortisone, cortisone, and corticosterone in man in vivo, in vitro, and the enzyme systems involved in the latter. 3) The turnover rate of endogenous hydrocortisone in man, and 4) the development of new methods for the determination of the corticosteroids and their metabolites in biological fluids.

Methods Employed: Pharmacological quantities of pure steroids and steroids labeled with Carbon-14 have been used to carry out many of these studies. Improved methods have been devised for the assay of steroids in micro quantities. Standard techniques have been used in the Carbon-14 assay work, and the work is now enzymology field.

Major Findings: In studies of the disposition of radiometabolites of hydrocortisone-4-C^{14} in rats and guinea pigs, it was shown that 35 per cent of the products were excreted in bile of rats in 3 hours whereas only 15 per cent appeared in the bile of guinea pigs in 3 hours. Though 65 per cent appeared in bile eventually in this species. The feces were the chief route of excretion in the rat, whereas the urine was the chief route in guinea pigs. In both species extensive enterohepatic circulation of labeled metabolites occurred. In neither species was the expired CO_2 labeled. The labeled substances were excreted in conjugated form.

Studies on disposition of hydrocortisone and cortisone in man have shown no difference in the rate of metabolic transformation of

trace and pharmacological quantities. A [illegible] metabolism of these [illegible] steroids has been shown [illegible] of an injected dose is metabolized in a normal person and [illegible] of these metabolites appear in the urine in 3 to 4 hours. [illegible] 30 per cent is excreted in the urine in 24 hours, and [illegible] cent has appeared by the end of 72 hours. Four per cent can be [illegible] counted for by fecal excretion. Practically no extrahepatic [illegible] tion exists, since studies in a bile fistula man have shown only 1 per cent excretion via this route. Studies on the rate of disappearance of hydrocortisone from the plasma have demonstrated in normal subjects that 50 per cent disappears in two hours however in [illegible] disease the steroid is metabolized much slower. In hyperthyroidism the steroid is metabolized more rapidly. Comparative studies with steroids structurally similar to hydrocortisone have shown that these steroids are metabolized more rapidly than hydrocortisone, and also that liver dysfunction does not impair their rates of metabolism.

A procedure has been developed for measuring the miscible pool of endogenous hydrocortisone, and its rate of turnover. Since hydrocortisone-4-C^{14} when injected intravenously in trace quantities disappears exponentially with time, it is possible to derive [illegible] ever data by calculating the hydrocortisone specific activity at various times following injection. Preliminary results suggest that the pool in a normal subject is 3 to 4 mg. and that this pool is turned over approximately 10 times per day.

Mechanism of Inactivation and Excretion of Adrenal Steroids

1. Enzymes have been isolated from animal liver which convert steroids to their inactive "tetrahydro" form. Two enzyme systems seem to be involved in this process of adding 4 hydrogen atoms to the steroid. The enzymes have been purified 150 fold and their properties and cofactors defined. This seems to be a general mechanism for steroid inactivation.

2. The manner in which the reduced or halogeno corticosteroids are subsequently conjugated as their glucuronides has been under study. The formation of the glucuronide serves to assist in the excretion of steroids in the urine by making them water soluble. It has been observed that an "active glucuronide donor" is necessary. This has been found to be a substance, uridine diphosphate glucuronic acid. This cofactor is found in liver and with the aid of an enzyme in the microsomes of liver transfers its glucuronic acid to the steroid.

Purification of the enzyme and studies on to its specificity are under investigation. However, it is apparent that uridine diphosphate glucuronic acid serves as a cofactor in the formation of many other glucuronides as well.

A new much more selective method for the determination of the urinary 17-ketosteroids has been developed. Studies are underway directed towards improvements in the methods for assay of the urinary

corticosteroids, especially in regard to improvements in the procedure for their quantitation. Various improvements in methods of use for determination of the plasma steroids have been developed. This has been applied to both the phenylhydrazine method, and the sulfuric acid-induced fluorescent methods.

Significance to NIAMD Research: The studies on physiological disposition and pharmacology are important in regard to the treatment of patients with steroids. The studies on in vivo and in vitro metabolism are needed to yield information related to steroid actions in biological systems. The studies on hormone [illegible] should make it possible for the first time to determine the actual production of hydrocortisone in the adrenals in various disease states and in normal subjects. The studies on methodology are necessary to make it possible to very reliably carry out all of these studies.

Proposed Course of Project: Additional data are needed on the disposition and pharmacology of corticosteroids, and other steroids, making growing therapeutic agents. Studies on the in vivo metabolism will be directed toward the enzyme systems involved in the conjugation of the steroid molecules, the corrective enzyme systems involved in steroid biotransformations, and certain enzymes involved in the synthesis of steroids in vivo. Studies on the in vivo biotransformation products of the steroids will be continued. A great deal of effort will be directed toward the quantitation of hydrocortisone turnover rate in normals and in disease states. Further work will be carried out on latter methods for the isolation and determination of the metabolites of the steroids by chromatographic methods.

15. USAEC - ORNL-96.
Title, Number

16. LIST PUBLICATIONS ISSUED DURING REPORTING PERIOD RESULTING FROM THIS PROJECT (January, 1954 - December, 1954):

Waggoner, J.E., Holt, A., and Peterson, S.R. Disposition of Intravenously Administered Ca^{45} in the Rat. U.S. A.E.C. In press.

17. LIST HONORS AND AWARDS RELATING TO THIS PROJECT AND ITS PERSONNEL DURING CALENDAR YEAR 1954:

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Arthritis and Rheumatism
LABORATORY

3. Diseases of the Blood
BRANCH

4. Bethesda
LOCATION

5. PHS - 6231-61
SERIAL NUMBER

6. The dynamics of red blood cell destruction and production in various types of anemia, normal males and females, and various laboratory animals.
PROJECT TITLE

7. Franklin C. Bowman, Jr., M.D.
PRINCIPAL INVESTIGATOR

8. Gerald P. Bochman, M.D.
OTHER INVESTIGATOR

9. PROJECT DESCRIPTION

Objectives: To develop a practical new technique for measuring rates of red blood cell destruction in a variety of anemic states and in normal man and animals, to establish normal values of red cell destruction in healthy male and female, and a number of animals, and to delineate the nature of anemia in hypothyroid states and iron deficiency anemia.

Methods Employed: Measurement of red blood survival in vivo by means of radioactive sodium chromate labeled red cells and their subsequent elimination and iron metabolism by radioactive tracer techniques and the combined determination of the above three components together with concurrent clinical studies.

Major Findings: Simultaneous employment of the radioactive sodium chromate technique and heavy isotopic techniques for measuring the life span of circulating red blood cells in vivo in humans as well as a wide variety of animals with normal and abnormal conditions have led to further information on the rate of elution of radiochromate from circulating red blood cells in vivo. The variation of red blood cells survival in normal females and males has been confirmed by the radioactive sodium chromate technique. The life span of red blood cells in the chicken, pigeon, and rat has been determined.

Significance to NIAMD Research: Based studies illustrate progress in the evaluation and development of a practical, safe, and reliable method for measuring red blood life span in humans and animals which eliminates the risk and practical limitations inherent in further widely used hemological techniques for studying rates of red blood

cell destruction. The speed of elution of sodium chromate from and a wide variety of diseased red blood cells in laboratory establishing the limits of usefulness and interpretation of results obtained with this new method of measuring red blood cell survival. The rates of red blood destruction determined in normal females and males are essential as a standard of comparison for findings in various diseased states. The length of survival in a wide variety of laboratory animals will be of fundamental histologic importance to the comparative physiologist and to studies of experimentally induced anemia in laboratory animals. It is hoped that studies on the cause of hypothyroidism and iron deficiency anemia will lead to a more complete understanding of the genesis of the anemia in these metabolic disorders.

Proposed Course of the Project: It is planned to expand the number and types of hemolytic syndromes studied with radioactive sodium chromate and further characterize the advantages and limitations of this new method. The type and number of normal control animals studied will be expanded.

10. HEW/HD - 6231-31
RURAL HOUSING

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	PROPOSED POSITIONS			MAN-YEARS			COMMENTS
		CAREER	OTHER	TOTAL	CAREER	OTHER	TOTAL	
FY 1955	10,100	2/3	1 1/3	4	8/3	5/6	2 1/2	
FY 1956	14,000	1	2	3	3/3	1 2/3	2	

12. BUDGET ACTIVITY:

RESEARCH ☒ DEMONSTRATION ☐
SERVICE & SPECIAL ☐ GRANT-IN-AID ☐

13. IDENTIFY ANY COOPERATIVE EFFORTS OF THE PUBLIC HEALTH SERVICE, OR OTHER AGENCIES, INCLUDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN 1955 or 1956. IF COOPERATING UNIT IS OUTSIDE PUBLIC HEALTH SERVICE, SPECIFY

None

14. IF THIS PROJECT DUPLICATES, COMPLEMENTS, OR PARALLELS RESEARCH/DEMONSTRATIONS IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (s) OF OTHER HRS)

None

35. NIAID - 62141-07

36. LIST PUBLICATIONS GIVING CREDIT FOR ASSISTANCE FROM THIS PROGRAM DURING CALENDAR YEAR 1952:

None

37. LIST HONORS AND AWARDS TO PERSONNEL RELATED TO THIS PROJECT DURING CALENDAR YEAR 1952:

None

Analysis of 24h urinary catecholamines

Digest Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigation
LABORATORY

3. Metabolic Diseases
BRANCH

4. Bethesda
LOCATION

5. ANAO-6213-98
GENERAL NUMBER

6. Studies in diabetes mellitus
PROJECT TITLE

7. J. D. Field
PRINCIPAL INVESTIGATOR

8. DeWitt Stetten, D. Sc.(Med.)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To study the relationship of dietary carbohydrate and fat to ketonuria in normal and diabetic subjects. To further study the mechanism of hyperglycemia unresponsiveness in cases of islet cell adenoma of the pancreas. To determine the presence of normal insulin antagonists in cases of insulin resistance, ketosis and infections complicating diabetes.

Methods Employed: Diabetics were given isocaloric diets with variations in the percentage of fat and carbohydrate. The effects of these alterations on ketonuria, insulin requirement, and presence of diabetic complications were observed.

Liver biopsies from patients with islet cell adenoma of the pancreas were analyzed for the amount and type of glycogen present. Similar experiments were carried out in rats who had been treated with insulin.

The ability of the rat rent-diaphragm to increase glycogen deposition under the influence of insulin is being used as a test system for normal insulin antagonists. Serum from diabetic ketotic cases will be tested.

Patient Material:

	No.	Average Stay (Days)
Adult males	4	57
Adult females	7	46
Child males	1	36

9. PROJECT DESCRIPTION - Continued

Major Findings: As a result of the dietary study it was shown that dietary carbohydrate influence ketone metabolism primarily by effects on hepatic ketogenesis. High fat intakes do not cause increased ketonuria in the well regulated diabetic, but may be dangerous in the labile diabetic. In the latter, high carbohydrate diets are of great therapeutic value. No relationship was found between the degenerative complications of diabetes and the pattern of ketonuria in response to changes in diet.

Studies on the hypoglycemic unresponsiveness seen in patients with islet cell adenomas seem to indicate that this phenomenon is related to a failure of glycogenolysis in the liver.

The test system involved in measuring insulin effect has been worked out.

Significance to NIAMD Research: The dietary study provides important information on the relationship of ketonuria alterations as diets to the metabolism of ketone bodies and control of the diabetic.

The studies on hypoglycemic unresponsiveness indicate the possible existence of an abnormality in the liver glycogen in patients with islet cell adenoma.

If humoral insulin antagonists are found, they might provide an explanation for the phenomenon of insulin resistance during the course of acidosis and infections in diabetics.

Proposed Course of Project: The serum of insulin resistant diabetics and those with infection and addicts will be studied to determine if they contain humoral insulin antagonists. If such a factor is found, attempts will be made to further characterize it.

10. [illegible]

XI. BUDGET DATA:

	ESTIMATED EXPENDITURES	ADVISED POSITIONS			MAN YEARS			PERSONS DAYS
		FIELD	OFFICE	TOTAL	FIELD	OFFICE	TOTAL	
FY 1955	4,900	1	1	2	1/3	1/2	5/6	686
FY 1956	3,900	1	1	2	1	1/2	1 1/2	700

XI. BUDGET ACTIVITY:

REGULAR	☒	ADMINISTRATIVE	☐
DEFICIT & OTHERS	☐	CONTINGENCY ARRANGEMENTS	☐

13. [illegible] ANY DEVELOPMENT PLANS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN CURRENT 1955 or 1956. IF COORDINATION HAS BEEN EFFECTED WITH PRIVATE AGENCIES, GIVE

None

14. IF FIELD SERVICE PERSONNEL, EQUIPMENT, OR FACILITIES PROVIDED UNDER AGREEMENT WITH PUBLIC HEALTH SERVICE/OTHERWISE INTERNATIONAL OR PERSONNEL, FACILITIES OR FUNDS), INDICATE SUCH RESOURCES. [illegible]

None

16. [illegible]

17. [illegible]

None

18. LIST HONORS AND AWARDS OF SCHOLARSHIP RECEIVED BY BILA PROJECT STAFF DURING CALENDAR YEAR 1954:

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations
LABORATORY

3. Surgery and General Metabolism
BRANCH

4. Metabolism
SECTION

5. NIAMD - Cell-Soy
CELL AGENT

6. Study of the Composition of Local Body Areas in Man
PROJECT TITLE

7. P. Harris, L. Hershenson
PRINCIPAL INVESTIGATOR(S)

8. E. Marsden, Dorothy Anderson
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To develop further a technique for use in the study of the composition of localized body areas as regards plasma, red blood cells and other constituents, and to study the effect on the composition of various disease states and therapeutic agents.

Methods Employed: Isotope dilution techniques, tracer substances, and techniques for the measurement of blood flow in various areas.

Patient Material: (25th calendar year)

Clinical Center Admissions:	No. of Pts.	Average Days Stay
Adult Males	2	4
Adult Females	3	4
Child Males	0	0
Child Females	0	0
Pts. also Hospitals	5	3
Georgetown University Hospital	7	3

Major Findings: A new technique has been further developed and applied to the quantitative measurement of plasma and red cell volumes of the splanchnic area in humans. It has been found that the volume of blood in the splanchnic area is sufficient to make it an important blood reservoir. The distribution of plasma and red cells in the splanchnic, ordinary and total body areas has been corroborated.

Significance to NIAMD Research: This method provides an approach to the study of the composition of local areas of the body in terms of various blood and extravascular components. It will aid in defining the alterations which occur in these constituents in various states, e.g., arthritis, diseases collagen etc.

Project Number 1-Z01-09

Project Chief(s) Henry Pollack

Proposed Course of Project: In connection of two studies to ascertain the effect of various disease states, such as rheumatoid arthritis, scleroderma and diabetes mellitus, changes known to be associated with alterations in total body composition will be studied in an effort to define the changes occurring in local areas such as the epicardiac bed. In addition to the study of these changes, the effects of various therapeutic agents will be investigated.

10. MIAMD - 6213-93
SOCIAL WORKER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PERM	OTHER	TOTAL	FTE USED PERM	OTHER	TOTAL	CHANGE
FY 1955	13,900	1	2	3	5/6	1 1/6	2	
FY 1956	17,900	1	2	3	1	2	3	+33

12. BUDGET ACTIVITY:

RESEARCH ☒ DEMONSTRATION ☐

DEVELOP & IMPROVED ☐ RESIDUAL SERVICES ☐

13. IDENTIFY AND DESCRIBE ANY OTHER SOURCES OF HEW FUNDS, HEALTH SERVICE, AND OTHER SOURCES, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL 1955 or 1956. IF COOPERATING UNIT IS OTHER THAN PROJECT DIRECTOR, SPECIFY:

None

14. IF THIS PROJECT RESULTS, EXPERIENCE, OR FINDINGS MIGHT BE USEFUL TO THE PUBLIC HEALTH SERVICE (WITHOUT EXPENDITURE OF ADDITIONAL PROJECT FUNDS), INDICATE SUCH USEFULNESS. (DO SEPARATE NO. (S) IF NEEDED SO.)

None

15. [illegible]

16. [illegible]
1954

None

17. [illegible]
1954

None

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations
LABORATORY

3. Metabolic Diseases
BRANCH

4. Bethesda
LOCATION

5. NIAMD-62131-100
SERIAL NUMBER

6. Studies related to thyroid function and disease
PROJECT TITLE

7. Dr. Paul A. Marks; Dr. Jacob Robbins; Dr. James E. Myngarden
PRINCIPAL INVESTIGATORS

8. Dr. Lee Hershenson; Miss Dorothea Jarzeng
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: A. To study the hepatic removal of serum protein-bound iodine in normal and abnormal states.

B. To study the mechanism of creatinuria and the metabolism of water and electrolytes in myxedema.

C. To determine the characteristics of protein binding of thyroid hormone in serum and other body fluids in normal and abnormal states.

D. To delineate the abnormalities in thyroid metabolism in patients with hypothyroidism associate with goiter.

E. To study iodine metabolism in thyroid homogenates.

Methods Employed: A number of separate techniques have been used in the above studies and include: hepatic catheterization in humans, metabolic balance determinations, renal clearances, some electrophoretic chromatography. Radioactive iodine has been used as a label in clinical studies, and in studying iodine metabolism in vivo.

Patient Material:

	No.	Average Stay (Days)
Adult males	1	4 (Hepatic catheterization study. Five of the 7 patients were admitted to Georgetown Univ. Hosp.)
Adult females	2	

9. Publications (continued)

Major Findings: A. The normal liver is capable of removing a large amount of the protein-bound iodine circulating through it, as determined by comparison of arterial and hepatic venous blood.

B. Thyroid homogenates, studied at 0°C, have the ability to utilize iodide, converting it to nonidentifiable and, especially, to an intermediate iodine compound extractable by carbon disulfide.

C. Technique for use in the other studies have been established.

Significance to NIAID Research: These studies represent new approaches to several aspects of thyroid physiology and disease. These include the secretion of hormone synthesis in the normal and diseased thyroid, the role of the liver in thyroid hormone metabolism, and the role of the specific thyroxine-binding protein in thyroid physiology.

Proposed Course of Project: The techniques which have been developed will be used to pursue further the problem listed above.

A.I.D. - 2
December 1955

10. MH(G)-A2130-1(C)
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	NUMBER OF POSITIONS			MAN YEARS			PROGRAM CODE
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$4,800	3	3	6	2 1/2	2 5/6	5 1/2	330
FY 1956	$3,200	4	3	7	4	3	7	330

12. PROJECT ACTIVITY:

RESEARCH [X] ADMINISTRATIVE [ ]

TRAINING [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY(S) 1955 or 1956. IF UNCOMPLETED UNIT IS WITHIN THE DEPARTMENT, GIVE NAME.

Dr. M. Shaker, NCI
Dr. J. D. Stanbury, Asst. Gen. Prep., Boston
Georgetown University Hospital

14. IF THIS PROJECT INVOLVES, SUPPLEMENTS, OR PARALLELS RESEARCH BEING CONDUCTED IN THE PUBLIC HEALTH SERVICE (WITHOUT EXCHANGE OF FUNDING, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH. (IF SERIAL NO.(S) IS KNOWN GIVE)

None

Semiannual Report of the Research Committee
(Research Reports and Publications Given)

15. NYO-1023-100
CONTRACT NUMBER

16. LIST TECHNICAL REPORTS ISSUED DURING CONTRACT PERIOD (Reports Listed Under Item 15)
1956:

Kregsamer, J. L., and J. H. Steinbach. "Formation of ethylcarbonate and an intermediate in the iodine complex by thyroid homogenates." J. Biol. Chem., Dec. 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATED TO THIS PROJECT DURING CONTRACT YEAR 1956:

None

1. National Institute of Arthritis and Metabolic Diseases
   U.S.P.H.S.

2. Clinical Investigations
   Laboratory

3. Section on Clinical Investigations
   Clinic

4. Laboratory
   Clinic

5. Clinic - Metro-Air
   Public Health

6. Studies of the effects of parathyroid hormone and of [illegible] on [illegible]
   and calcium in man.
   PROJECT TITLE

7. Howard L. Bleed and David G. Bronson
   PRINCIPAL INVESTIGATOR

8. G. D. Jensen
   Other Key Personnel

9. PROJECT DESCRIPTION

   Objectives: The objectives of this research are to elucidate [illegible]
   the parathyroid hormone in relation to [illegible]
   the normal subject and in patients with [illegible]
   osteoarthritis and to study the factors regulating the [illegible]
   parathyroid gland in normal subjects and in those with [illegible].

   Methods Employed: The renal clearance of calcium and [illegible]
   before and after the administration of parathyroid extract
   and under the influence of several dietary [illegible]
   [illegible]. The relationship of dietary calcium to [illegible]
   and of dietary [illegible] to calcium balance [illegible]
   normal persons and in patients with [illegible]. [illegible]
   [illegible] by radioactive calcium [illegible]. In addition, the [illegible]
   of calcium in the urinary [illegible] of [illegible] has been studied
   in this [illegible].

   Patient Materials

	No.	Average Daily Visits
Adult males	5	5
Adult females	7	13
Children, M/F	0	
Newborn, M/F	2	2
Not Outpatient		[Number of Visits]

   Major Findings: The capacity of parathyroid hormone to [illegible]
   function has been demonstrated. A relationship between [illegible]
   calcium and [illegible] and the reabsorptive capacity of the [illegible]

[illegible] (Project Description, Clinical Investigation)

tionale for phosphorus was used found in normal subjects. Preliminary studies on the role of the parathyroid glands in bone metabolism have been carried out.

Significance to NIAMD Research: The diagnosis of diseases of the parathyroid glands is hindered by the absence of specific tests of parathyroid function. This is particularly important in patients who have bone disease of unknown etiology and in those who repeatedly form renal calculi. The diagnosis and removal of parathyroid tumors in many such patients leads to permanent cure. It is hoped that information obtained in the present studies may lead to more specific methods of diagnosis in such patients. In addition, an attempt will be made to elucidate the function of the parathyroid glands in patients with such diseases of bone as osteoporosis and osteomalacia.

Proposed Course of Project: The studies in normal subjects will be continued. In addition these methods will be employed in the investigation of patients with bone disease, with renal stones, and with known or suspected disorders of parathyroid function. In addition will be made to determine the rate of endogenous parathyroid hormone secretion under normal and abnormal conditions. Finally, the mechanism of action of parathyroid hormone will be investigated in tissue explanted in vitro studies.

10. [illegible] - 6213-002

11. [illegible] DATA:

	[illegible]	Students Served			FTE Staff			[illegible]
	[illegible]	Male	Female	Total	Male	Female	Total	
FY 1965	37,400	1	2	3	1 2/3	3 1/3	5 1/6	60
FY 1966	43,400	2	4	6	2	4	6	300

12. [illegible] ACTIVITY:

[illegible] ☑ [illegible] ☐

[illegible] ☐ [illegible] ☐

13. [illegible] [illegible] [illegible]

15. [illegible] - 52.53-101
[illegible]

16. [illegible] [illegible] [illegible] [illegible] [illegible] [illegible]
1954

None

17. [illegible] [illegible] [illegible] [illegible] [illegible] [illegible]
1954

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations
LABORATORY

3. Arthritis & Mineral Metabolism
BRANCH

4. Bethesda
LOCATION

5. NIAMD-AMLM-100
SERIAL NUMBER

6. Effects of diet and steroid hormones on mineral metabolism in patients with bone disease.
PROJECT TITLE

7. G. D. Whedon; H. H. Platt
PRINCIPAL INVESTIGATORS

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To investigate the practical aspects of therapy with oral steroid hormones of various types of demineralizing bone diseases. This involves study of the metabolic effectiveness and dosage of oral steroid preparations, their effective dosage levels, and the relationship of the latter to accomplishing or terminating osteoporosis.

Methods Employed: Metabolic balance determinations, roentgenographic techniques.

Patient material:

	No.	Average Stay (hours)
Adult Female	1	240
Children female	1	96

Major Findings: In the single female patient with osteoporosis studied over an extended period necessary, the effectiveness and desirability of oral androgen and estrogen in promoting the storage of bone salts and protein. Significant accomplishing side-effects did not occur.

Significance to NIAMD Research: Remineralization of the skeleton is a common accompaniment at all ages, including rheumatoid arthritis. Although the value of the steroid hormones administered parenterally has been demonstrated, therapy by this route has generally been abandoned after a brief trial due to inconvenience. If a practicable regimen for the necessarily long period (months) of hormone administration in treatment of these bone disorders can be developed from the demonstration of effectiveness of the oral route, a valuable aid in the chronic care of many patients will be provided.

1. National Institutes of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations
LABORATORY

3. Section on Mineral Metabolism
BRANCH

4. Bethesda
LOCATION

5. AM-04213-20A
GRANT NUMBER

6. Effects of diet and steroid hormones on mineral metabolism in patients with bone disease.
PROJECT TITLE

7. G. D. Wheelon; H. H. Hiatt
PRINCIPAL INVESTIGATORS

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To investigate the practical aspects of therapy with diet and steroid hormones of various types of demineralizing bone disease. This involves study of the metabolic effects[illegible] the clinical results of oral steroid preparations, their effective dosage levels, and the relationship of the latter to mineralizing or demineralizing effects.

Methods Employed: Metabolic balance determinations, which mean intensive techniques.

Patient Material:

	No.	Average Stay (Days)
Adult Female	1	240
Children female	1	90

Major Findings: In the single female patient with osteoporosis studied over an extended period necessary, the effectiveness was demonstrated of oral androgen and estrogen in promoting the storage of both salts and protein. Significant mineralizing side-effects did not occur.

Significance to NIAMD Research: Demineralization of the skeleton is a constant accompaniment at all ages, including rheumatoid arthritis. Although the value of the steroid hormones administered parenterally has been demonstrated, therapy by this route has usually been abandoned after a brief trial due to inconvenience. If a practical regimen for the necessarily long period (months) of hormone administration in treatment of these bone disorders can be developed from the demonstration of effectiveness of the oral route, a valuable aid to the chronic care of many patients will be provided.

5. PROJECT DESCRIPTION - Continued

Proposed Course of Project: Several additional methods will need to be utilized by the available behavior technique to prove the effectiveness of oral steroid hormones. The studies will include efforts to define more closely the effective dosage levels and to determine to what extent androgens and estrogens moderate one another's side-effects while supplementing one another's desirable effects.

A.P.O. —
Deadline: 7:30

10. CLASSIFICATION:
SPECIAL OTHER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			GRADES
		THIS	OTHER	TOTAL	THIS	OTHER	TOTAL	THIS
FY 1955	16,700	1	2	3	1	1 1/2	2.0	10
FY 1956	19,700	1	2	3	1	2	3	10

12. BUDGET ACTIVITY:

CLEARANCE ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ PERSONAL OBSERVATION ☐

13. IDENTIFY THE GOVERNMENTAL UNITS OF THE PUBLIC HEALTH SERVICE OR OTHER ORGANIZATIONS, INCLUDING FUNDS, FACILITIES, OR PERSONNEL FOR WHICH PROJECT IS BEING DONE OR WILL BE DONE DURING FY 1955 or 1956. IF OPERATIONS ARE OF LITTLE OR NO IMPORTANCE SAY SO. (NOTE)

None

14. IF THIS PROJECT CONCERNS, OR IS LIKELY TO CONCERN, RELATIONS WITH PERSONNEL IN THE PUBLIC HEALTH SERVICE (WITHOUT DESIGNATION OF PERSONS, POSITIONS OR OFFICE), IDENTIFY SUCH RELATIONS. (SEE SPECIAL NOTE) IF WITHDRAWN

None

[illegible]

[illegible]

[illegible]

15. [illegible]

9

16. [illegible]

None

17. [illegible]

None

1. Arthritis Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Clinical Investigations
DIVISION

3. [illegible]

4. Energy and Clinical Nutrition
BRANCH

5. Bethesda
LOCATION

6. NIAMD - 04131-103
CHECK NUMBER

7. Total energy metabolism; studies in health and disease
PROJECT TITLE

8. G.D. Wadden
PRINCIPAL INVESTIGATOR

9. Ernest E. Howe, M.D.
OTHER INVESTIGATOR

10. PROJECT DESCRIPTION

Objectives: 1) To establish to complete annual measurement a technique to measure energy balance which can be applied to various clinical problems and to fundamental physiological problems of energy metabolism and new approaches; 2) To study the influence on total energy expenditure and balance of various factors, including climate and the endocrine hormones; 3) To investigate the characteristics of energy expenditure and their influence on the maintenance state of patients in chronic disease conditions, such as obesity and cancer.

Methods Employed: Indirect human calorimetry by means of sophisticated equipment in the respiratory chamber, metabolic balance techniques, caloric analysis of dietary intake and of excreta.

Major Findings: During the past calendar year the shell of the respiration chamber has been completed, and the installation and testing of the air-conditioning apparatus has been partially completed. The hygrometers, recorders, valves and pumps are being assembled and tested.

Significance To NIAMD Research: Studies of total energy metabolism have not been carried out previously. [illegible] figures for the daily caloric requirement in various categories are based either on food consumption data or on brief measurements of activity metabolism extrapolated to twenty-four hours. The respiration chamber, therefore, when long periods of time, in which considerable exact measurements total calories expended, is a unique facility.

As an example of the type of problem that can be approached in a new way with the chamber is the condition obesity or overweight, which predisposes individuals to the development of diabetes, heart disease, and possible high blood pressure and arteriosclerosis.

It may be possible for the first time to determine whether or not an intrinsic metabolic difference exists between lightweight and heavy-eating, thin individuals. This information might lead the way toward development of effective treatment or prevention of this serious affliction.

Proposed Course of Project: Work will be begun this year with normal individuals at [illegible] in determining the [illegible] energy expenditure in certain common activities of daily living. [illegible] in establishing the technique of energy balance. When these [illegible] are well established, clinical studies will follow.

10. NYMSO - 6213-12
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			P.H. YEARS			FTE
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	9,100	1	1	2	1/2	1	1 1/2	—
FY 1956	12,100	1	1	2	1	1	2	—

12. BUDGET ACTIVITY:

ASSESSED ☒ ADMINISTERED ☐

PLANNED & APPROVED ☐ PROVISIONAL REQUESTED ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL 1955 OR 1956. IF COOPERATING UNIT IS STATE OR LOCAL AGENCY, SPECIFY IF:

None

14. IF THIS PROJECT ASSOCIATES, CONSULTANTS, OR FELLOWSHIPS ARE INVOLVED IN THE PUBLIC HEALTH SERVICE EXTENSION ORGANIZATION, [illegible] FUNDS), INDICATE SUCH ASSISTANCE FOR FISCAL YEAR (S) IN QUESTION:

None

15. [illegible]
[illegible]

16. [illegible]
1954:

None

17. [illegible]
[illegible] 1954:

None

15. [illegible] - [illegible]
[illegible]

16. [illegible]
1926.

None.

17. [illegible]
[illegible] 1926.

None.

10. [illegible] (PPIL-100)
[illegible]

11. [illegible]:

	CAPITAL EXPENDITURES	PROJECTED POSITIONS			MAN-YEARS			
		PMS	Other	Total	PMS	Other	Total	
FY 1955	11,500	1	2	3	1/3	2	2 1/3	
FY 1956	14,600	1	2	3	1	2	3	

12. BUDGET ACTIVITY:

[illegible] ☒ [illegible]

[illegible] ☐ [illegible]

13. [illegible] [illegible] [illegible]

15. [illegible]

16. [illegible]
1954:

None

17. [illegible]
1954:

None

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Biochemistry and Nutrition
SECTION

3. Biochemistry and Physiology of Amebiasis
BRANCH

4. Bethesda
LOCATION

5. NIAMD - 62A3-10S
SPECIAL NUMBER

6. Nitrogen balance in normal adults on modified Kempner rice-fruit diet(s) with amino acid supplements.
PROJECT TITLE

7. Harold H. Sandstead and James M. Hundley
PRINCIPAL INVESTIGATORS

8. Donald G. Weedon
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To determine whether the nutritive value of rice can be improved by the addition of amino acids.

Methods Employed: (1) Measurement of nitrogen equilibrium by determination of nitrogen balance on constant non-supplemented and supplemented rice-fruit diets (2500 calories with 40 gm. protein daily from 450 gm. rice, plus fruit and sugar.)
(2) Measurement of urea excretion in plasma and urine on the same dietary regimen.

Patient Material: (1954 Calendar Year)

	No.	Inpatient Days Used
Admissions:	Whole males (normal	1	100

Major Findings: (1) The data suggested that lysine and threonine favored attainment of nitrogen equilibrium in two of three normal males, but the changes were small and of doubtful significance.
(2) Methionine was not additive to the effect of lysine and threonine.

Significance to NIAMD Research: This is an attempt to (1) eliminate one of the undesirable features of a nutritionally useful diet, e.g., the sustained negative nitrogen balance of the rice-fruit diet, and (2) improve a staple food.

Proposed Course of Project: An extension of the project is planned whereby how do these normal subjects fit acceptance on

10. AID/W - STATE-US
SOCIAL SCIENCE

11. BUDGET DATA:

	OBLIGATED REPRESENTATIVES	REQUIRED POSITIONS			AID FUNDS			OTHER
		PASA	OTHER	TOTAL	PASA	OTHER	TOTAL	
FY 1955	20,300	1 1/3	2/3	2	1 1/3	2/3	2	
FY 1956	25,000	2	1	3	2	1	3	

12. BUDGET ACTIVITY:

ABSENCE [X] INTERVENTION [ ]

REVIEW & APPROVAL [ ] CONTRACT NEGOTIATION [ ]

13. INDICATE ANY CONSIDERED NEEDS IN THE PUBLIC HEALTH SECTOR [illegible] SUCH AS SCHOOLS, PROVISION FUNDS, FACILITIES, OR PERSONNEL AND [illegible] 1955 or 1956. IF ACCEPTABLE ONLY IS FUNDS AID PROJECT [illegible]

None

14. IF THIS PROJECT RECEIVES, [illegible] OR FINANCIAL ASSISTANCE [illegible] IN THE PUBLIC HEALTH SERVICE (WITHOUT [illegible] OF FUNDS, [illegible] FUNDS), INDICATE HOW [illegible] (IN SPECIAL [illegible] IF [illegible]

None

15. [redacted]
[redacted]

16. [redacted]
1951

None

17. [redacted]
[redacted] 1951

None

Project Description Sheet

1. National Institute of Arthritis and Metabolic Diseases
INSTITUTE

2. Office of Director
LABORATORY

3.
DIVISION

4.
SECTION

5. Z1AM-57111-306
SERIAL NUMBER

6. Administration
PROJECT TITLE

7. Dr. Floyd S. Daft; Mr. W. G. Berlie
PRINCIPAL INVESTIGATORS

8. Mr. D. A. Brandner
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The major responsibility of the Office of the Director is to provide the overall executive direction and coordination of the laboratory, clinical and grants programs in order to achieve the objectives of the Institute, namely the conducting and supporting of research investigations concerned with the cause, diagnosis, treatment and prevention of arthritis, rheumatism and metabolic diseases. This immediate program direction is supplemented further by maintaining close relationships with national medical and scientific, as well as lay groups and non-Federal institutions, such as the Arthritis and Rheumatism Association, the Arthritis and Rheumatism Foundation, and the American Diabetes Association, which are interested in dealing with the medical and economic problems posed by these disorders.

The Office of the Director includes a small staff which assists in furnishing the executive direction and administrative management services to the laboratory, clinical and extramural programs staff of the Institute.

Significant Contributions: During the past year the National Institute of Arthritis and Metabolic Diseases was host to numerous meetings and conferences held at the Clinical Center by private medical, scientific and lay organizations. These included, the National Conference on Research and Education in the Rheumatic Diseases, sponsored by the American Rheumatism Association, the Arthritis and Rheumatism Foundation and the National Institute of

9. PROGRESS DESCRIPTION - Continued

Arthritis and Metabolic Diseases, the First Interim Scientific Session of the American Rheumatism Association, and the annual Meeting of the D. C. Chapter of the Arthritis and Rheumatism Foundation. The staff of the Director's Office handled all of the preliminary arrangements regarding space, invitations, hotel reservations, printing of programs, tours of the Clinical Center and exhibits in the Laboratory and Clinical Areas of NIAMD in the Clinical Center.

In the past year the position of Associate Director in Charge of Research was created and filled through the employment of Dr. DeWitt Stetten Jr., an outstanding scientist in the field of Intermediary metabolism. By the end of the year the integration of this position into the Institute's framework has been accomplished and a most satisfactory management pattern has evolved and has proven most effective in providing the necessary coordination of the Laboratory Research and Clinical Investigations areas of activity.

Another project which involved considerable effort was the preparation of plans for laboratory alterations in Buildings 3 and 10 as well as formulation of plans for the space of the various organizational segments of the Institute that will be involved. Some of these renovations and moves have already been accomplished.

10. NIAID-57LL-3G6
SERIAL NUMBER

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	CONTRACT DAYS
FY 1955	$62,100	4	6	10	4	6	10	-
FY 1956	$62,100	4	6	10	4	6	10	-

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☒

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FISCAL YEAR 1955 OR 1956. IF COOPERATING UNIT IS WITHIN THE PHS GIVE SERIAL NO(S)

None

14. IF THIS PROJECT REQUIRES, PURCHASES, OR PARALLELS RESEARCH BEING CONDUCTED IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH. (GIVE SERIAL NO(S) IF WITHIN PHS)

None

Instructions on U.S. Progress Reports

Patents, Awards and Publications Sheet

15. NIAID-67111-106
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

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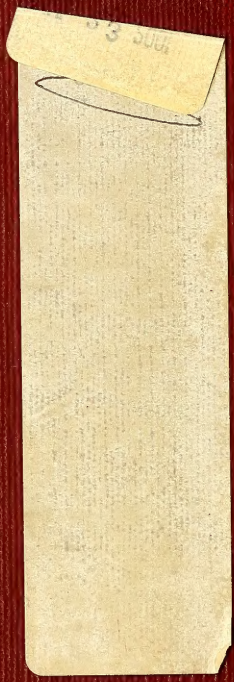
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